ISSN 0003-2999
Volume 64, Number 9, September 1985

Acc.
9.12.86

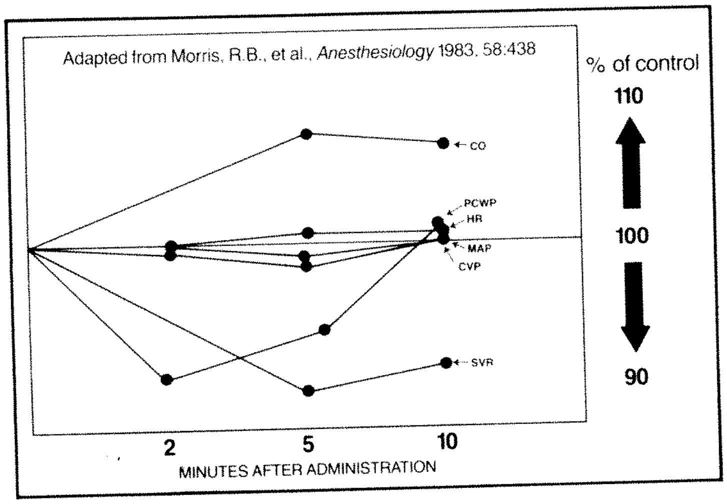
# Anesthesia and Analgesia

⑫

Journal of the International Anesthesia Research Society
Oldest Publication in the Specialty—Established 1922

## In neuromuscular blockade...

# Closest to the ideal:


Adapted from Morris, R.B., et al., *Anesthesiology* 1983, 58:438

### Free of clinically significant cardiovascular effects

NORCURON is the only surgical muscle relaxant for which no clinically significant adverse cardiovascular effects have been observed in clinical trials.[1-3] This makes NORCURON unique among all neuromuscular blocking agents in clinical use.[4]

The Effect of Non-depolarizing Muscle Relaxants on Histamine Levels, Mean Arterial Pressure and Heart Rate[5]

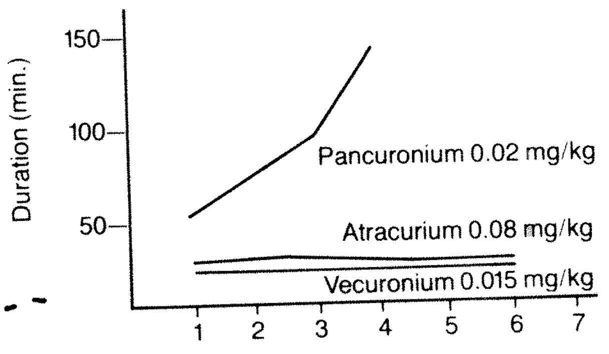
| | | | Percent of Control | | |
|---|---|---|---|---|---|
| Drug | Dose (mg/kg) | xED$_{95}$ | Histamine | Mean Arterial Pressure | Heart Rate |
| tubocurarine | 0.5 | 1 | 318 | 78 | 116 |
| metocurine | 0.5 | 2 | 212 | 79 | 119 |
| atracurium | 0.6 | 3 | 192 | 80 | 108 |
| vecuronium | 0.1 | 1.7 | 117 | 100 | 99 |
| vecuronium | 0.2 | 3.5 | 87 | 99 | 102 |

### Histamine release unlikely to occur

Histamine release has not been observed with NORCURON...as shown by preliminary clinical experience. In doses up to 3.5 times the ED$_{95}$, it causes no increase in circulating histamine nor does it decrease systemic blood pressure.[5]

Hypotension and tachycardia tend to occur when histamine levels are increased to about 200% of control.[5]

The Neuromuscular Effects of Maintenance Doses of Vecuronium, Atracurium and Pancuronium[6,7]



### No clinically significant cumulative effects seen

With NORCURON cumulative effects are not seen in clinical practice. The interval between repeated doses has been found to remain constant between as many as six to ten repeated administrations.[6,7]

P24582
CU6-H04029-12-P024582

# NORCURON®

## (vecuronium bromide for injection)

| Safety Index and Comparative Safety Ratios[8] | | | |
|---|---|---|---|
| Safety Index = $\frac{\text{ED}_{50}\text{ autonomic inhibition}}{\text{ED}_{95}\text{ neuromuscular blockade}}$ | | | |
| Comparative Safety Ratios | | | |
| For Vagolytic Effects | | For CV/Histamine Related Effects | |
| gallamine | 1:1 | d-tubocurarine | 1:1 |
| pancuronium | 3:1 | metocurine | 2:1 |
| atracurium | 25-30:1 | atracurium | 3:1 |
| vecuronium | 60:1 | vecuronium | * |

*cannot be calculated since it does not cause any CV or histamine related effects

## Outstanding safety profile

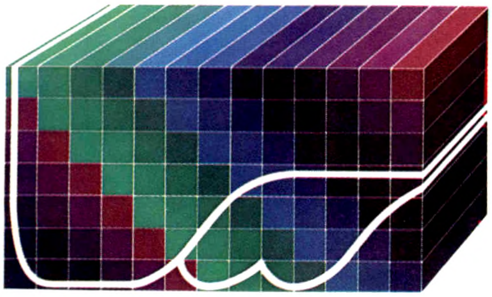
The Safety Index helps quantify the improved safety of the newer muscle relaxants on a relative basis. The characteristics of cardiovascular effects and histamine release are areas where the new agents, particularly NORCURON, have made the most significant gains.[8]

The Safety Index is described as the $\text{ED}_{50}$ for autonomic inhibition over the $\text{ED}_{95}$ for neuromuscular blockade.[8]

A Comparison of Surgical Muscle Relaxants vs. The Ideal[4]
(" + " signifies proximity to the ideal)

| Characteristic | Vecuronium | Atracurium | Pancuronium | Succinylcholine | D-tubocurarine |
|---|---|---|---|---|---|
| Onset of Action | – | – | – | + | – |
| Histamine Release | + | – | + | + | – |
| Cardiovascular Side Effects | + | +/– | – | – | – |
| Duration of Action | + | + | – | + | – |
| Cumulative Effects | + | + | – | – | – |
| Rate of Recovery | + | + | – | + | – |
| Reversibility | + | + | + | – | + |
| Potency | + | + | + | – | – |
| Non-depolarizing | + | + | + | – | + |
| Metabolite Activity | + | +* | + | + | + |

*Currently under evaluation.



**NORCURON®**
(vecuronium bromide for injection)

## Closest to the ideal

Of the newer short- to intermediate-acting drugs, NORCURON has the most ideal profile, specifically attributable to its outstanding safety features relating to cardiovascular side effects and histamine-releasing properties.[4]

Organon

**References**

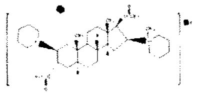
**1.** Durant NN: Norcuron* — A new non-depolarizing neuromuscular blocking agent. *Semin Anesth* 1:47-56, 1982. **2.** Morris RB, Cahalan MK, Miller RD, et al: Cardiovascular effects of vecuronium (ORG NC45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 58:438-440, 1983. **3.** Krieg N, Crul JF, Booij LH: Relative potency of ORG NC45, pancuronium, alcuronium, and tubocurarine in anaesthetized man. *Br J Anesth* 52:783-787, 1980. **4.** Miller RD (ed): *Innovations in Surgical Muscle Relaxants*. Far Hills, NJ, Gardiner-Caldwell Synermed, 1984. **5.** Basta SA, Savarese JJ: Comparative histamine-releasing properties of vecuronium, atracurium, tubocurarine and metocurine, in Agoston S, et al (eds): *Clinical Experiences with Norcuron (ORG NC45, vecuronium bromide)*. Amsterdam, Excerpta Medica, 1983, p. 183. **6.** Foldes FF, et al: Muscular relaxation with atracurium, vecuronium and Duodor under balanced anaesthesia. *Br J Anaesth* 55 (suppl. 1): 97S, 1983. **7.** Fahey MR, Morris RB, Miller RD, et al: Clinical pharmacology of ORG NC45 (Norucon*): a new non-depolarizing muscle relaxant. *Anesthesiology* 55:6, 1981. **8.** Clinical Courier, Vol. 2, No. 4, July 1984.

# NORCURON® (NC-45)

Vecuronium Bromide for Injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

**DESCRIPTION:** NORCURON* (vecuronium bromide for injection) is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[(2β, 3α, 5α, 16β, 17β)-3, 17-bis (acetyloxy)-2-(1-piperidinyl) androstan-16-yl]-1-methyl-, bromide. The structural formula is



Norcuron* is supplied as a sterile freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic.

**CLINICAL PHARMACOLOGY:** Norcuron* (vecuronium bromide for injection) is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron* is about 1/3 more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron* is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The $ED_{90}$ (dose required to produce 90% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron* dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron* is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron* is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron* (vecuronium bromide for injection) may be decreased by approximately 15% (see Dosage and Administration Section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron* and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron* will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron*, the administration of Norcuron* should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron* has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron* has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to a 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron* neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started the neuromuscular block produced by Norcuron* (vecuronium bromide for injection) is readily reversed with various anticholinesterase agents, e.g. pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron* induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

**Pharmacokinetics:** At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron* is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35-40 minutes. The volume of distribution at steady state is approximately 300-400 ml/kg; systemic rate of clearance is approximately 3-4.5 ml/minute/kg. In man, urine recovery of Norcuron* varies from 3-35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron* has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of the injected dose; 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron* (vecuronium bromide for injection); equipotent doses are of approximately the same duration as Norcuron* in dogs and cats. Biliary excretion accounts for about half of the dose of Norcuron* within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron*. Limited data derived from the patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron* in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary-capillary-wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease.) Limited clinical experience (3 patients) with use of Norcuron* during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron* (vecuronium bromide for injection) has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

**INDICATIONS AND USAGE:** Norcuron* is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

**CONTRAINDICATIONS:** None known.

**WARNINGS:** NORCURON* SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron* may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

**PRECAUTIONS:**

**Renal Failure:** Norcuron* (vecuronium bromide for injection) is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron* should be considered.

**Altered Circulation Time:** Conditions associated with slower circulation time in cardiovascular disease, old age, or edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

**Hepatic Disease:** Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in recovery from Norcuron* metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTENT EXCESS DOSING.

**Severe Obesity or Neuromuscular Disease:** Patients with severe obesity or neuromuscular disease may pose ai way and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blockir agents such as Norcuron* (vecuronium bromide for injection).

**Malignant Hyperthermia:** Many drugs used in anesthetic practice are suspected of being capable of triggering potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient dat derived from screening in susceptible animals (swine) to establish whether or not Norcuron* is capable of tric gering malignant hyperthermia.

Norcuron* has no known effect on consciousness, the pain threshold or cerebration. Administration must b accompanied by adequate anesthesia.

**Drug Interactions:** Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Nor curon* and its duration of action. If succinylcholine is used before Norcuron*, the administration of Norcuron should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intuba ing agent, initial doses of 0.04-0.06 mg/kg of Norcuron* may be administered to produce complete neuromusc lar block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY).

The use of Norcuron* (vecuronium bromide for injection) before succinylcholine, in order to attenuate some of tl side effects of succinylcholine, has not been sufficiently studied. Other nondepolarizing neuromuscular blockin agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron* therefore these drugs and Norcuron* may manifest an additive effect when used together. There are insufficie data to support concomitant use of Norcuron* and other competitive muscle relaxants in the same patient.

**Inhalational Anesthetics:** Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane wi Norcuron* will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane an isoflurane.

With the above agents the initial dose of Norcuron* may be the same as with balanced anesthesia unless the inha lational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equil brium (see CLINICAL PHARMACOLOGY).

**Antibiotics:** Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produc a neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced anti biotics are used in conjunction with Norcuron* (vecuronium bromide for injection) during surgery, unexpecte prolongation of neuromuscular block should be considered a possibility.

**Other:** Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggest that recurrent paralysis may occur. This possibility must also be considered for Norcuron*. Norcuron* induce neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, eithe enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia o pregnancy, may enhance neuromuscular blockade.

**Drug/laboratory test interactions:** None known.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals have not been performed tc evaluate carcinogenic or mutagenic potential or impairment of fertility.

**Pregnancy: Pregnancy Category C:** Animal reproduction studies have not been conducted with Norcuron*. It i also not known whether Norcuron* can cause fetal harm when administered to a pregnant woman or can affec reproduction capacity. Norcuron* should be given to a pregnant woman only if clearly needed.

**Pediatric Use:** Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron* (vecuronium bromide for injection) on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

**ADVERSE REACTIONS:** Norcuron* was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron* as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron* is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

**OVERDOSAGE:** There has been no experience with Norcuron* overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation. Excessive doses of Norcuron* (vecuronium bromide for injection) can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron* as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve. Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol* (pyridostigmine bromide injection), neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron*. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

**DOSAGE AND ADMINISTRATION:** Norcuron* (vecuronium bromide for injection) is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron* by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain the maximum clinical benefits of Norcuron* and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron* is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the $ED_{90}$) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3.0 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron* (vecuronium bromide for injection) is enhanced. If Norcuron* is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron* dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron*. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron* to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron* are recommended; after the initial Norcuron* injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron* lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained (see CLINICAL PHARMACOLOGY).

**Dosage in children:** Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron* (vecuronium bromide for injection) on a mg/kg basis than adults and take about 1½ times as long to recover. See also sub-section of PRECAUTIONS titled Pediatric use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS).

**COMPATIBILITY:** Norcuron* is compatible in solution with

- 0.9% NaCl solution
- 5% glucose in water
- 5% glucose in saline
- Lactated Ringers

**HOW SUPPLIED:** 5 ml vials (contains 10 mg of active ingredient) and 5 ml ampul of preservative-free sterile water for injection as the diluent. Boxes of 12. NDC 0052-0442-10

**STORAGE:** PROTECT FROM LIGHT. Store at 15°-30°C (59°-86°F).

**AFTER RECONSTITUTION:** Solution may be stored in refrigerator or kept at room temperature not to exceed 30°C (86°F). DISCARD SOLUTION AFTER 24 HOURS. DISCARD UNUSED PORTION.

SINGLE USE VIALS — Manufactured for ORGANON INC. By BEN VENUE LABORATORIES, INC., Bedford, Ohio 44146

**ORGANON PHARMACEUTICALS**, a Division of
Organon Inc. West Orange, N.J. 07052

# Anesthesia and Analgesia

## Journal of the International Anesthesia Research Society

3645 Warrensville Center Road, Cleveland, Ohio 44122 Telephones: (216) 295-1124 or 295-1130

## Editorial Board

### Editor in Chief

Nicholas M. Greene, MD, New Haven, Connecticut

### Editors

David R. Bevan, MA, MB, BChir, Montreal, Quebec, Canada
D. Ryan Cook, MD, Pittsburgh, Pennsylvania
Michael J. Cousins, MD, FFARACS, FFARCS, Adelaide, South Australia
Benjamin G. Covino, PhD, MD, Boston, Massachusetts
Norig Ellison, MD, Philadelphia, Pennsylvania
Mieczyslaw Finster, MD, New York, New York
Alison B. Froese, MD, Kingston, Ontario, Canada
Edward D. Miller JR, MD, Charlottesville, Virginia
Daniel M. Philbin, MD, Boston, Massachusetts
Cedric Prys-Roberts, MA, DM, PhD, Bristol, United Kingdom
J. Gerald Reves, MD, Durham, North Carolina
John H. Tinker, MD, Iowa City, Iowa
K.C. Wong, PhD, Salt Lake City, Utah

### Book Review Editor

Norig Ellison, MD, Philadelphia, Pennsylvania

Editorial correspondence and manuscripts should be addressed to: NICHOLAS M. GREENE, MD, Editor in Chief, *Anesthesia and Analgesia,* Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510 (Telephone: 203-785-4703). For information concerning preparation of manuscripts see "A Guide for Authors" published quarterly in the Journal. All articles published in this Journal become the property of the International Anesthesia Research Society. Reproduction in whole or part is not permitted cept by written consent of the publisher and the author.

s for review should be sent directly to the Book Review Editor, IG ELLISON, MD, Department of Anesthesia, University of nnsylvania, Philadelphia, Pennsylvania 19104.

eprints: For single copies, write directly to the senior author at the address listed on the title page. Quantity orders (minimum 100) processed through ELSEVIER SCIENCE PUBLISHING CO, INC, 52 Vanderbilt Avenue, New York, NY 10017, prices on request.

The International Anesthesia Research Society is a nonprofit, scientific, and educational corporation in the state of Ohio. Members of the Board of Trustees of the Society are: Douglas B. Craig, MD, Bruce F. Cullen, MD, E. Paul Didier, MD, Judith H. Donegan, MD, PhD, Noel W. Lawson, MD, John T. Martin, MD, Emerson A. Moffitt, MD, Dean H. Morrow, MD, Robert K. Stoelting, MD, and John L. Waller, MD. Emeritus Trustees are: Paul R. Dumke, MD, Kenneth K. Keown, MD, Morris T. Nicholson, MD, B.B. Sankey, MD, and T. H. Seldon, MD.

*Anesthesia and Analgesia* (ISSN 0003-2999) is issued monthly for the IARS in one indexed volume per year by Elsevier Science Publishing Co, Inc, 52 Vanderbilt Avenue, New York, NY 10017. Printed in USA. © 1985 International Anesthesia Research Society. Second class postage paid at New York, NY and at additional offices.

Subscription information for 1985 applying to IARS members: USA and possessions, $45.00 per year, in all other countries $55.00. Membership is available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine, or other disciplines who are engaged in active clinical practice of or research in anesthesiology. ASSOCIATE MEMBERSHIP is available to individuals certified, licensed, or accredited in anesthesia-related professions (CRNA, CRTT, RRT, Physician Assistant). EDUCATIONAL MEMBERSHIP (half the full member price) is available to interns, residents, students in nurse anesthesia and related training programs, for a 2- or 3-year period only upon completion of application including certification by applicant's program director.

All membership payments and correspondence regarding IARS member subscriptions should be sent to: Emerson A. Moffitt, MD, Executive Secretary, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, Ohio 44122.

Subscription information for 1985 applying to non-IARS members: Institutions, $90.00. Outside of the USA and possessions, please add $10.00 for surface postage and handling. For airmail, add $38.00 in USA, Canada, and Mexico, $22.00 for surface airlift to Europe, $34.00 for surface airlift to Japan, and $88.00 for airmail to the rest of the world. Postmaster: Send address changes to: *Anesthesia and Analgesia,* Elsevier Science Publishing Co, Inc, 52 Vanderbilt Avenue, New York, NY 10017.

Orders and inquiries regarding institutional and nonmember individual subscriptions should be directed to: Journals Fulfillment, Elsevier Science Publishing Co, Inc, 52 Vanderbilt Avenue, New York NY 10017. Subscriptions are entered for the calendar year, January–December.

Correspondence inquiries regarding IARS member subscriptions should be sent to the IARS at the Cleveland, Ohio address above. Correspondence regarding all other subscriptions should be sent to Elsevier.

Advertising inquiries should be addressed to: Pharmaceutical Media, Inc, 130 Madison Avenue, New York, NY 10016. The appearance of advertising in publications of the International Anesthesia Research Society does not constitute a guarantee or endorsement of the quality or value of such product or of the claims made for it by its manufactuer. Discussions, views, and recommendations as to medical procedures, choice of drugs, and drug dosages are the responsibility of the authors. Every effort has been made to ensure the accuracy of the information. The editor, publisher, or the Society, however, must disclaim any responsibility or liability. Readers are advised to check package insert information for each drug before administration.

See classified ads section for submission of classified material.

Single issues: Single copy information available from Elsevier Science Publishing Co, Inc, upon request. Back volume (all issues prior to 1983) information available from IARS.

Anesthesia
and Analgesia

# Contents

**Volume 64, Number 9, September 1985**

## EDITORIAL

Fresh Frozen Plasma: Too Few Indications—Too Much Use *Joseph R. Bove* 849

## SCIENTIFIC ARTICLES

Morphine–Caffeine Analgesic Interaction in Rats *Donald L. Person, Igor Kissin, Pamela T. Brown, Anne V. Xavier, H. Ronald Vinik, and Edwin L. Bradley* 851

Analgetic Contribution of Sufentanil during Halothane Anesthesia: A Mechanism Involving Serotonin *John S. Althaus, Edward D. Miller, Jeffrey C. Moscicki, Bernice R. Hecker, and Cosmo A. DiFazio* 857

Response Differences of Paretic and Healthy Extremities to Pancuronium and Neostigmine in Hemiplegic Patients *Hiroshi Iwasaki, Akiyoshi Namiki, Keiichi Omote, Tetsuo Omote, and Takeo Takahashi* 864

A Comparison of Edrophonium and Neostigmine for the Antagonism of Atracurium-Induced Neuromuscular Block *Gavin G. Lavery, Rajinder K. Mirakhur, and Fiona M. Gibson* 867

Etomidate versus Thiopental for Induction of Anesthesia *Jeffrey L. Giese, Randall J. Stockham, Theodore H. Stanley, Nathan L. Pace, and Rob H. Nelissen* 871

A Comparison of Fentanyl–$O_2$ and Sufentanil–$O_2$ for Cardiac Anesthesia *Michael B. Howie, Thomas D. McSweeney, Rao P. Lingam, and Stuart P. Maschke* 877

Intraoperative Changes in Blood Coagulation and Thrombelastographic Monitoring in Liver Transplantation *Yoo Goo Kang, Douglas J. Martin, Jose Marquez, Jessica H. Lewis, Franklin A. Bontempo, Byers W. Shaw, Thomas E. Starzl, and Peter M. Winter* 888

Comparison of Morphine, Meperidine, Fentanyl, and Sufentanil in Balanced Anesthesia: A Double-Blind Study *Joan W. Flacke, Byron C. Bloor, Benjamin J. Kripke, Werner E. Flacke, Christine M. Warneck, Aaron P. Van Etten, David H. Wong, and Ronald L. Katz* 897

Bupivacaine Cardiovascular Toxicity: Comparison of Treatment with Bretylium and Lidocaine *Gregory W. Kasten and Stuart T. Martin* 911

Differential Spread of Blockade of Touch, Cold, and Pinprick during Spinal Anesthesia *Angelo G. Rocco, Stephen A. Raymond, Ellen Murray, Usha Dhingra, and Dubravka Freiberger* 917

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY
WE STRIVE ALWAYS FOR WORLD CONQUEST OF PAIN
1922

## SCIENTIFIC ARTICLES—*continued*

Hemodynamic and Plasma Catecholamine Responses to Epinephrine-Containing Perianal Lidocaine Anesthesia — *W. Byron Barber, Lee E. Smith, Gary P. Zaloga, J. Raymond Fletcher, David Cook, C. Raymond Lake, and Bart Chernow* 924

Morphine Concentration in Brain and Spinal Cord after Subarachnoid Morphine Injection in Baboons — *M. A. Gregory, J. G. Brocke-Utne, S. Bux, and J. W. Downing* 929

## CLINICAL REPORTS

Myocardial Ischemia due to Obstruction of an Aortocoronary Bypass Graft by Intraoperative Positioning — *Chris M. Weinlander, Dennis W. Coombs, and Stephen K. Plume* 933

Paraplegia Caused by Spinal Angioma—Possible Association with Epidural Analgesia — *Nicholas P. Hirsch, Christopher S. Child, and S. A. Wijetilleka* 937

## LETTERS TO THE EDITOR

Balanced Anesthesia: Does it Anesthetize? — *Ian F. Russell* 941

A Bellow's Leak in an Ohio Anesthesia Ventilator — *Charles H. Ripp and James W. Chapin* 942

Ordering Priorities: Improved Anesthesia or Surgery—the Case of Cordotomy — *Perry G. Fine* 942

Myoclonus on Recovery from Etomidate — *Mark D. Tasch* 943

Cost of Muscle Relaxant Drugs — *J. Antonio Aldrete and Peter L. Hendricks* 943

Anaphylactoid Reaction to Pancuronium — *D. A. Moneret-Vautrin and M. C. Laxenaire* 944

**Albumin & PPF are no safer or more effective than Hespan®**

(hetastarch)

*...they're simply*

©1985 American Critical Care

## As safe as albumin or PPF

In comparative clinical studies, platelet counts, hematocrits, serum fibrinogen levels, prothrombin times (PT), and partial thromboplastin times (PTT) seen with Hespan were comparable to those seen with albumin or plasma protein fraction (PPF).[1,2]

Other studies demonstrate that when any reduction in platelet count or prolongation of PT or PTT does occur with Hespan, no increased bleeding results, even in patients with multiple trauma.[3-5] As with any volume expander, patients should be monitored for excessive hemodilution of coagulant factors or circulatory overload when large volumes are administered.

When Hespan-treated patients were monitored to detect localized or systemic sepsis, there was no evidence of a decrease in their ability to ward off infection or combat an established infection.[5]

Hespan is nonantigenic and, as with blood-derived colloids, any risk of allergic reaction is minimal. Hespan also has a negligible effect on subsequent blood typing or crossmatching.[6]

## As effective as albumin or PPF

Comparative clinical studies have repeatedly demonstrated that Hespan is as effective as albumin or PPF in postoperative myocardial revascularization,[1-3] and hemorrhagic, traumatic, or septic shock.[4,5,7]

No significant differences between Hespan and albumin or PPF were noted in any efficacy parameter.[1-5,7] Hespan effectively maintained colloid osmotic pressure, restored plasma volume, and improved cardiac output and renal function in hypovolemic patients.[1-5,7] And, the volume-expanding effect of a single infusion of Hespan can persist for 24 hours or longer.

## Half the price of albumin or PPF

Hespan offers a potential savings to your hospital of tens of thousands of dollars a year.

*double the price.*

Hespan
(6% hetastarch in 0.9% sodium chloride injection)
Hespan
6% hetastarch in 0.9% sodium chloride injection
Hespan (Hetastarch)

For additional information, contact the Medical Services Department, American Critical Care, 1600 Waukegan Road, McGaw Park, IL 60085. Phone 1-800-323-4980.

**Lifesaving, moneysaving**

# HESPAN®
# (hetastarch)

**American Critical Care**

American Hospital Supply Corporation

*Please see references and brief summary of prescribing information on following page.*

**References:** **1.** Diehl JT, Lester JL, Cosgrove DM: Clinical comparison of hetastarch and albumin in postoperative cardiac patients. *Ann Thorac Surg 34* (6):674-679, 1982. **2.** Moggio RA, Rha CC, Somberg ED, et al: Hemodynamic comparison of albumin and hydroxyethyl starch in postoperative cardiac surgery patients. *Crit Care Med 11* (12):943-945, 1983. **3.** Kirklin JK, Lell WA, Kouchoukos NT: Hydroxyethyl starch versus albumin for colloid infusion following cardiopulmonary bypass in patients undergoing myocardial revascularization. *Ann Thorac Surg 37* (1):40-46, 1984. **4.** Puri VK, Paidipaty B, White L: Hydroxyethyl starch for resuscitation of patients with hypovolemia and shock. *Crit Care Med 9* (12):833-837, 1981. **5.** Shatney CH, Deepika K, Militello PR, et al: Efficacy of hetastarch in the resuscitation of patients with multisystem trauma and shock. *Arch Surg 118*:804-809, 1983. **6.** Daniels MJ, Strauss RG, Smith-Floss AM: Effects of hydroxyethyl starch on erythrocyte typing and blood crossmatching. *Transfusion 22* (3):226-228, 1982. **7.** Rackow EC, Falk JL, Fein IA, et al: Fluid resuscitation in circulatory shock: A comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. *Crit Care Med 11*(11):839-850, 1983.

# HESPAN® (hetastarch)

## 6% Hetastarch in 0.9% Sodium Chloride Injection

***CONTRAINDICATIONS***

Hetastarch is contraindicated in patients with severe bleeding disorders or with severe congestive cardiac and renal failure with oliguria or anuria.

***WARNINGS***

Large volumes may alter the coagulation mechanism. Thus, administration of hetastarch may result in transient prolongation of prothrombin, partial thromboplastin and clotting times. With administration of large doses, the physician should also be alert to the possibility of transient prolongation of bleeding time.

Hematocrit may be decreased and plasma proteins diluted excessively by administration of large volumes of hetastarch.

***Usage in Leukapheresis:*** Significant declines in platelet counts and hemoglobin levels have been observed in donors undergoing repeated leukapheresis procedures due to the volume expanding effects of hetastarch. Hemoglobin levels usually return to normal within 24 hours. Hemodilution by hetastarch and saline may also result in 24 hour declines of total protein, albumin, calcium and fibrinogen values.

***Usage in Pregnancy:*** Reproduction studies have been done in mice with no evidence of fetal damage. Relevance to humans is not known since hetastarch has not been given to pregnant women. Therefore, it should not be used in pregnant women, particularly during early pregnancy, unless in the judgment of the physician the potential benefits outweigh the potential hazards.

***Usage in Children:*** No data available pertaining to use in children.

The safety and compatibility of additives have not been established.

***PRECAUTIONS***

The possibility of circulatory overload should be kept in mind. Special care should be exercised in patients who have impaired renal clearance since this is the principal way in which hetastarch is eliminated. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Indirect bilirubin levels of 0.83 mg% (normal 0.0-0.7 mg%) have been reported in 2 out of 20 normal subjects who received multiple hetastarch infusions. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering hetastarch to patients with a history of liver disease.

Regular and frequent clinical evaluation and laboratory determinations are necessary for proper monitoring of hetastarch use during leukapheresis. Studies should include CBC, total leukocyte and platelet counts, leukocyte differential count, hemoglobin, hematocrit, prothrombin time (PT), and partial thromboplastin time (PTT).

Hetastarch is nonantigenic. However, allergic or sensitivity reactions have been reported (see ADVERSE REACTIONS). If such reactions occur, they are readily controlled by discontinuation of the drug and, if necessary, administration of an antihistaminic agent.

***ADVERSE REACTIONS***

The following have been reported: vomiting, mild temperature elevation, chills, itching, submaxillary and parotid glandular enlargement, mild influenza-like symptoms, headaches, muscle pains, peripheral edema of the lower extremities, and anaphylactoid reactions consisting of periorbital edema, urticaria, and wheezing.

***HOW SUPPLIED***

NDC **0094-0037-05-Hespan*** (6% Hetastarch in 0.9% Sodium Chloride Injection) is supplied sterile and nonpyrogenic in 500 ml intravenous infusion bottles.

***CAUTION***

Federal (U.S.A.) law prohibits dispensing without prescription.

Rev: Feb., 1982

Distributed by

**American Critical Care**

American Hospital Supply Corporation
McGaw Park, IL USA 60085

---

## A Valuable Source of Information on Diagnostic Imaging:

CT

# THE JOURNAL OF COMPUTED TOMOGRAPHY

Editor-in-Chief: **Franklin L. Angell, M.D.,**
Chairman, Department of Radiology, Mercy
Hospital, Baltimore, Maryland

A quarterly publication, ***CT: The Journal of Computed Tomography*** highlights advances in the clinical application of imaging modalities. Articles by leading radiologists compare the cost-effectiveness, diagnostic yield, and appropriateness of the various imaging techniques (plain film, ultrasound, nuclear medicine, NMR, and angiography) to diagnose disease in the head and body. Issues include

- case reports
- book reviews
- abstracts from the literature
- meeting and conference announcements.

***CT*** is an important news source and essential reading for physicians who use diagnostic imaging.

**1985 Subscription Information**

Volume 9 (4 issues)

Institutional Rate: $104.00 Personal Rate $52.00

For air delivery in the U.S.A., Canada, or Mexico, add $12.00. Subscribers outside the U.S.A. should add $9.00 for surface delivery (not available to Europe); $10.00 for surface air lift delivery to Europe; or $26.00 for air delivery to the rest of the world. Subscribers in Japan must add $14.50 for delivery (via surface air lift only).

For a free sample copy, send to:

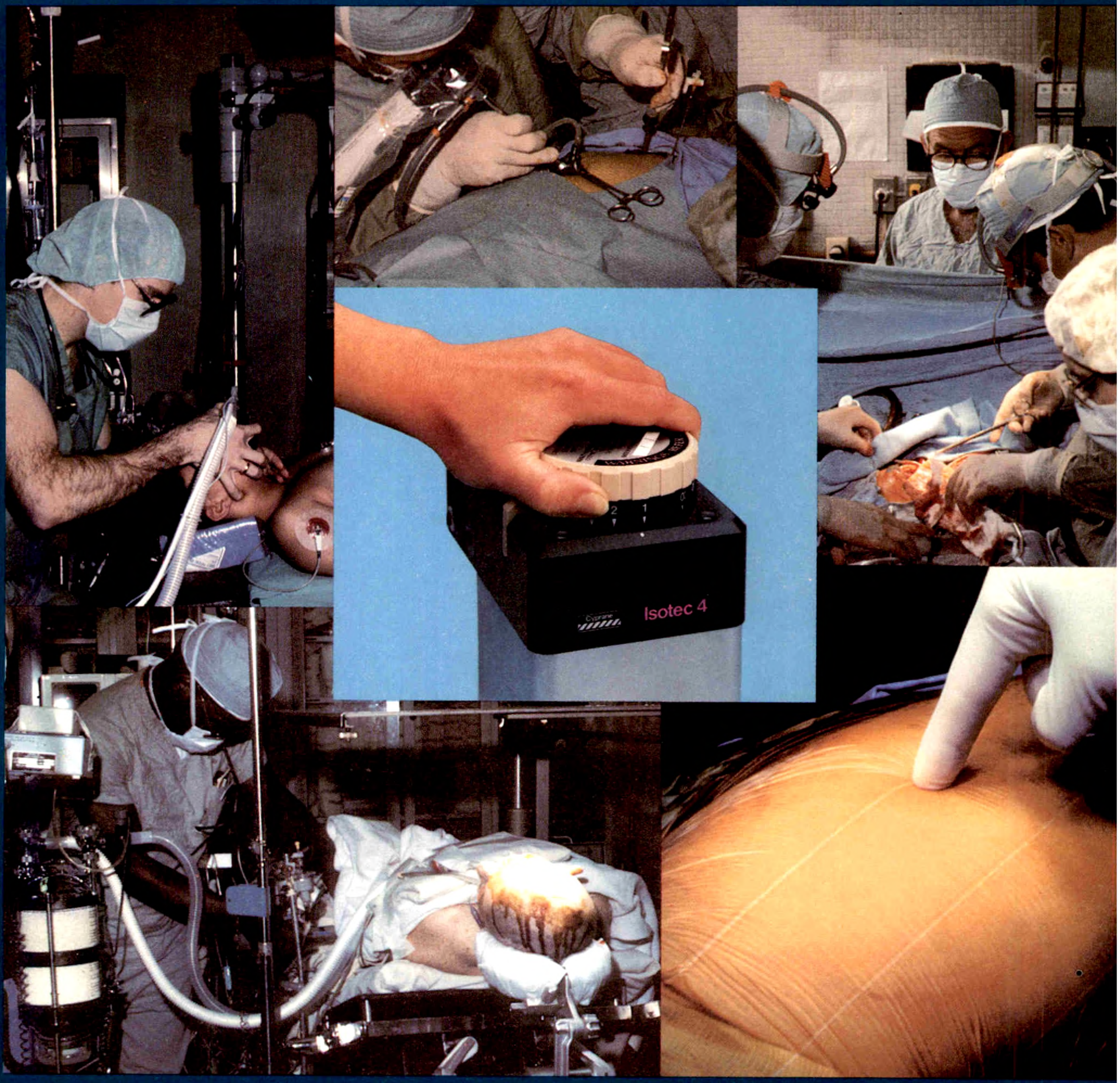
in North and South America:
**Elsevier Science Publishing Co., Inc.**
P.O. Box 1663
Grand Central Station
New York, NY 10163
in the rest of the world:
**Elsevier Science Publishers**
Direct Mail Department
P.O. Box 211
1000 AE Amsterdam
The Netherlands

**Note: All subscription orders should be sent either to your usual supplier or to the New York address.**

**ELSEVIER**

All subscriptions begin with the first issue of the calendar year. Personal subscriptions must be prepaid. Subscription rates valid through December 31, 1984.

Forane® (isoflurane)
The Versatile Anesthetic



**Anaquest**

Forane® (isoflurane)

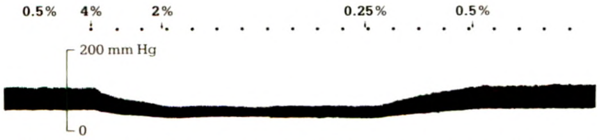
BOC Health Care

© 1984 BOC Inc

# Forane® (isoflurane)
# The Versatile Anesthetic

## A hypotensive agent for craniotomy and clipping of aneurysms

Isoflurane may be used as both anesthetic and hypotensive agent, providing for precise control of blood pressure throughout procedures such as clipping of cerebral aneurysms.[1]



Plood pressure tracing demonstrating the rapid response of systemic blood pressure to changes in inspired isoflurane concentration. The arrows indicate the changes in isoflurane concentration and the dots mark 1-min intervals. Mean blood pressure during the normotensive period was 70 mm Hg and 40 mm Hg during the hypotensive phase.[1]

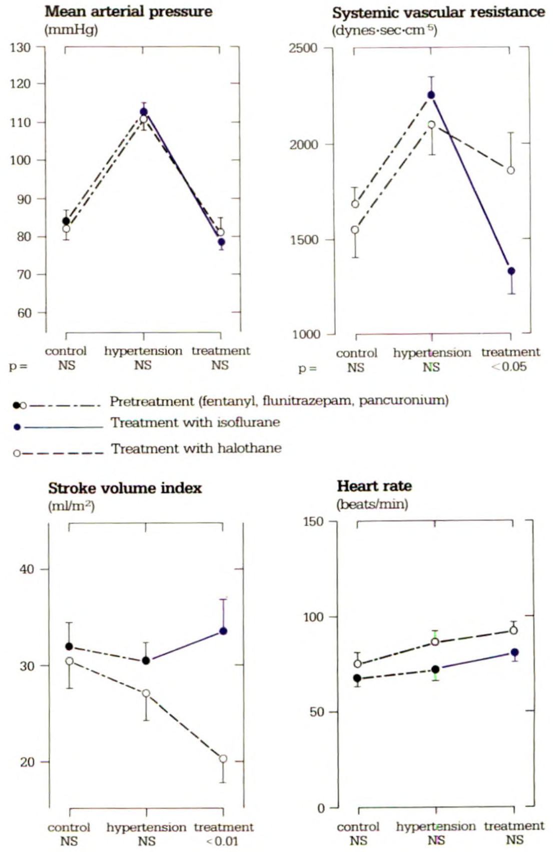
## Control of intracranial pressure for craniotomy and excision of space-occupying lesion

Isoflurane causes no increase in intracranial pressure (ICP) when $PaCO_2$ is controlled at 25-30 torr, and ICP may be readily lowered *during surgery* by decreasing $PaCO_2$.[2]

## Control of hypertension during coronary artery bypass surgery

Control of intraoperative hypertension may be achieved with isoflurane by lowering peripheral vascular resistance (left ventricular afterload) generally without depressing stroke volume or increasing heart rate. These effects can be of particular benefit in patients with compromised left ventricular function. Halothane is equally effective in lowering blood pressure without increasing heart rate, but it decreases stroke volume.

Treatment of hypertension with either isoflurane or halothane anesthesia in patients undergoing coronary artery bypass surgery (Adapted from Hess et al[3]).



## Potentiation of relaxants for orthopedic surgery

With isoflurane anesthesia, profound surgical muscle relaxation can be provided with one-third to two-thirds the usual relaxant dose (pancuronium, d-tubocurarine or atracurium).[4,5] Thus the recovery period may be shortened and the need for reversal agents reduced by the rapid elimination of isoflurane.

## Stability of heart rhythm when full hemostatic doses of epinephrine are needed

"Isoflurane, like enflurane, produces stable cardiac rhythm and, unlike halothane, does not sensitize the myocardium to the effects of catecholamines."[6]

## A rapid recovery with few post-anesthetic symptoms for outpatient surgery

"Isoflurane is eliminated more rapidly than any other potent modern inhaled anesthetic."[7] (Blood-gas partition coefficient, only 1.4)

Anesthesia using isoflurane in a mixture of oxygen and air produced a significantly lower incidence of nausea and vomiting following outpatient laparoscopy than anesthesia that included nitrous oxide.[8]

**Post-laparoscopy Nausea (N) and Vomiting (V)**

| Group | No. of Patients | No. of Patients with N or N&V |
|---|---|---|
| fentanyl, $N_2O$, $O_2$ | 37 | 23 (62%)* |
| isoflurane, fentanyl, $O_2$ | 20 | 6 (30%) |
| isoflurane, $O_2$ | 20 | 5 (25%) |

Adapted from Alexander et al[8] *$p<0.05$

**References:**

1. Lam AM, Gelb AW: Cardiovascular effects of isoflurane-induced hypotension for cerebral aneurysm surgery. Anesth Analg 62:742-748, 1983.
2. Adams RW et al: Isoflurane and cerebrospinal fluid pressure in neurosurgical patients. Anesthesiology 54:97-99, 1981. 3. Hess W et al: Comparison of isoflurane and halothane when used to control intraoperative hypertension in patients undergoing coronary artery bypass surgery. Anesth Analg 62:15-20, 1983. 4. Miller RD et al: Comparative neuromuscular effects of pancuronium, gallamine, and succinylcholine during Forane and halothane anesthesia in man. Anesthesiology 35:509-514, 1971. 5. Tracrium® (atracurium besylate) prescribing information, Burroughs Wellcome Co., Research Triangle Park, NC 27709. 6. Wade JG, Stevens WC: Isoflurane: an anesthetic for the eighties? Anesth Analg 60(9):666-682, 1981.
7. Eger EI II: Isoflurane, a compendium and reference, Ohio Medical Anesthetics, Madison, WI, 1981. 8. Alexander GD et al: The role of nitrous oxide in postoperative nausea and vomiting. Anesth Analg 63:175, 1984.

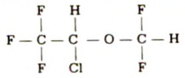
For complete use information, please see following page.

**Forane® . . . a product of original Anaquest research**
**(isoflurane)**

# Forane®...The Versatile Anesthetic
## (isoflurane)

CAUTION: Federal Law Prohibits Dispensing without Prescription

**DESCRIPTION:** FORANE (isoflurane) is a nonflammable general inhalation anesthetic agent. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:



$$\mathrm{F{-}\underset{F}{\overset{F}{C}}{-}\underset{Cl}{\overset{H}{C}}{-}O{-}\underset{F}{\overset{F}{C}}{-}H}$$

Some physical constants are:

| | | |
|---|---|---|
| Molecular weight | | 184.5 |
| Boiling point 760 mm Hg. | | 48.5°C (Uncorr.) |
| Refractive index $n_D^{20}$ | | 1.2990—1.3005 |
| Specific gravity 25°/25°C | | 1.496 |
| Vapor pressure in mm Hg.** | 20°C | 238 |
| | 25°C | 295 |
| | 30°C | 367 |
| | 35°C | 450 |

**Equation for vapor pressure calculation:

$$\log_{10} P_{vap} = A + \frac{B}{T} \quad \text{where: } A = 8.056,\ B = -1664.58,\ T = °C + 273.16 \text{ (Kelvin)}$$

| | |
|---|---|
| Partition coefficients @ 37°C | |
| Water/gas | 0.61 |
| Blood/gas/gas | 1.43 |
| Oil/gas | 90.8 |
| Partition coefficients @ 25°C—rubber and plastic | |
| Conductive rubber/gas | 62.0 |
| Butyl rubber/gas | 75.0 |
| Polyvinylchloride/gas | 110.0 |
| Polyethylene/gas | ~2.0 |
| Polyurethane/gas | ~1.4 |
| Polyolefin/gas | ~1.1 |
| Butyl acetate/gas | ~2.5 |
| Purity by gas chromatography | >99.9% |
| Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec. and 23°C | None |
| Lower limit of flammability in oxygen or nitorus oxide at 900 joules/sec and 23°C | Greater than useful concentration in anesthesia. |

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave U.V. light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

**CLINICAL PHARMACOLOGY:** FORANE (isoflurane) is an inhalation anaesthetic. The M.A.C. (minimum alveolar concentration) in man is as follows:

| Age | 100% Oxygen | 70% $N_2O$ |
|---|---|---|
| 26 ± 4 | 1.28 | 0.56 |
| 44 ± 7 | 1.15 | 0.50 |
| 64 ± 5 | 1.05 | 0.37 |

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation of tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal $PaCO_2$, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administerd epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 ml of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE, THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

**Pharmacokinetics:** Isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

**INDICATIONS AND USAGE:** FORANE (isoflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

**CONTRAINDICATIONS:** Known senitivity to FORANE (isoflurane) or other halogenated agents. Known or suspected genetic susceptibility to malignant hyperthermia.

**WARNINGS:** Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions.

FORANE (isoflurane) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

**PRECAUTIONS: General:** As with any potent general anesthetic, FORANE (isoflurane) should only be administered in an adequately equipped anesthetizing enivronment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

**Information to Patients:** Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

**Laboratory Tests:** Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

**Drug Interactions:** Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and M.A.C. (minimum alveolar concentration) is reduced by concomitant administration of $N_2O$. See Clinical Pharmacology.

**Carcinogenesis:** Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at $\frac{1}{2}$, $\frac{1}{8}$, and $\frac{1}{32}$ M.A.C. for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice which were given the same background gases, but not the anesthetic.

**Pregnancy Category C:** Isoflurane has been shown to have possible anesthetic-related fetotoxic effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

**Malignant Hyperthermia:** In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the $CO_2$ absorption system (hot canister). $PaO_2$ and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

**ADVERSE REACTIONS:** Adverse reactions encountered in the administration of FORANE (isoflurane) are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting, and ileus have been observed in the postoperative period.

As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia.

**OVERDOSAGE:** In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

**DOSAGE AND ADMINISTRATION: Premedication:** Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

**Inspired Concentration:** The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for isoflurane;
b) vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula

$$\%\ \text{isoflurane} = \frac{100\, P_V F_V}{F_T (P_A - P_V)}$$

where $P_A$ = Pressure of atmosphere
$P_V$ = Vapor pressure of isoflurane
$F_V$ = Flow of gas through vaporizer (ml)
$F_T$ = Total gas flow (ml)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

**Induction:** Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbituate. Inspired concentrations of 1.5 to 3% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

**Maintenance:** Surgical levels of anesthesia my be sustained with a 1.0-2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5% to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

**HOW SUPPLIED:** FORANE (isoflurane), NDC 10019-360-40, is packaged in 100 ml amber-colored bottles.

**Storage:** Store at room temperature. Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

Revised 1-83

**Anaquest** Forane® (isoflurane)

Anaquest
2005 West Beltline Highway
Madison WI 53713 2318
608 273 0019
Telex 910 286 2792
A Division of BOC Inc

**BOC Health Care**

Form No. 04-0086-A01
Printed in USA

# DIFFICULT INTUBATIONS MADE EASIER.

## INTRODUCING THE AFFORDABLE, FLEXIBLE LARYNGOSCOPE

The improved Flexible Laryngoscope now offers many advantages of the expensive bronchoscope, including suctioning — at about one third the cost!

The brilliant fiber optic illumination and 120° end-tip deflection allow the constant visualization required for rapid nasal/oral intubations.

When the intubation is complete, the 50 cm flexible length is gently withdrawn, leaving the endotracheal tube precisely positioned.

The portable LS-7 offers a cost-effective advantage for every anesthesiology department.

AA-9

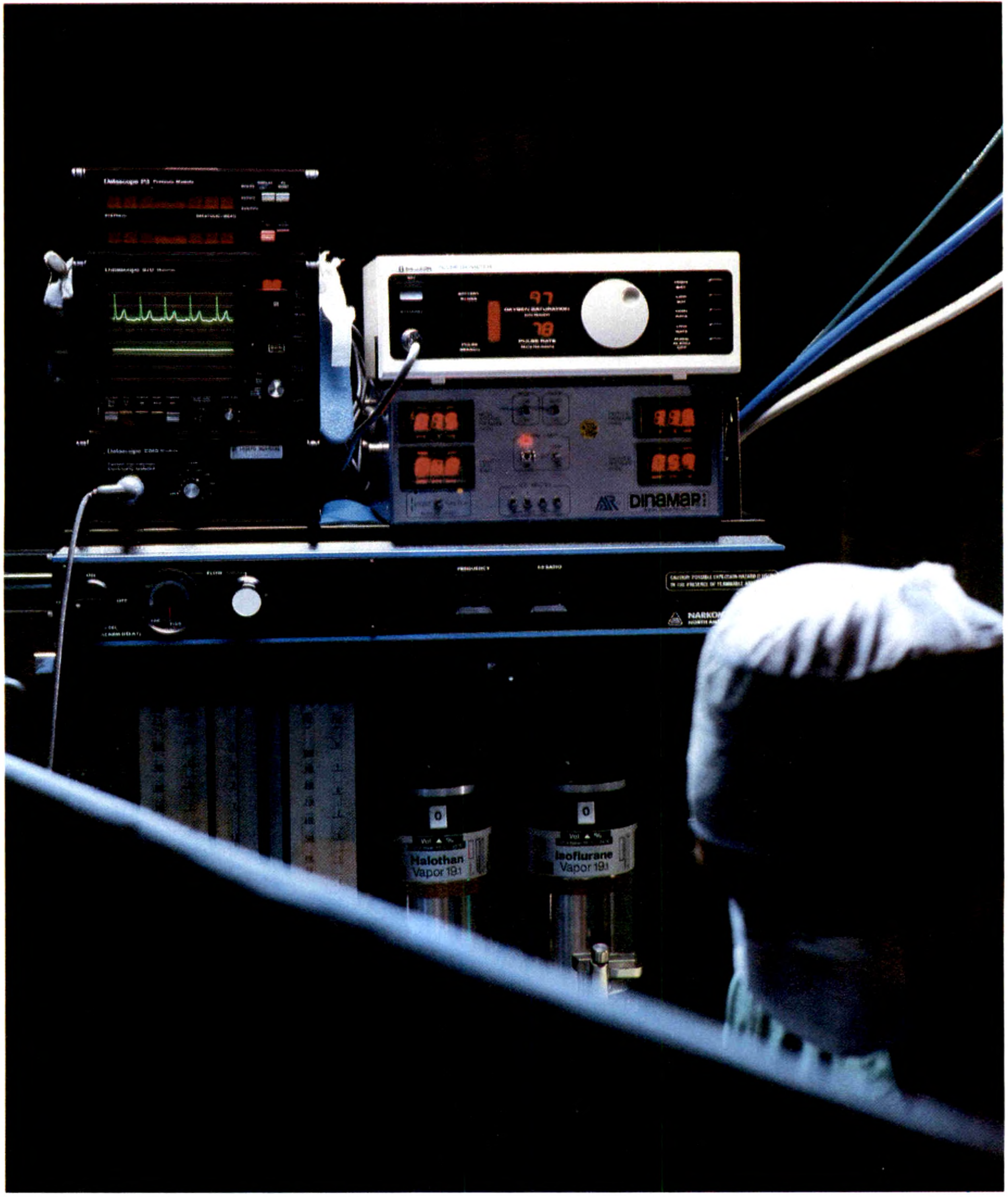
☐ Send further information on the LS-7
☐ Contact me to arrange a demonstration
The best hours to reach me are ____________
Name ____________
Street Address ____________
City ____________ State ____________ Zip ____________
Phone ____________

Reichert Fiber Optics
122 Charlton St., Southbridge, MA 01550
617/765-9744

**Reichert®**

**Reichert Fiber Optics**
Warner-Lambert Technologies, Inc.
122 Charlton Street
Southbridge, MA 01550

See us at ASA Booth #539


Datascope P3
97
OXYGEN SATURATION
78
PULSE RATE
DINAMAP
Halothan
Vapor 19.1
Isoflurane
Vapor 19.1

# Setting the standard in hypoxemia monitoring.

## The Nellcor® N-100 pulse oximeter.

**Now, for patient safety in all cases... all the time.**

Leading clinicians in major medical centers use the Nellcor N-100 pulse oximeter. Over thirty-five published papers* document the need for this monitor.

By continuously monitoring arterial oxygen levels, the Nellcor N-100 can detect patient hypoxemia before it results in adverse outcome.

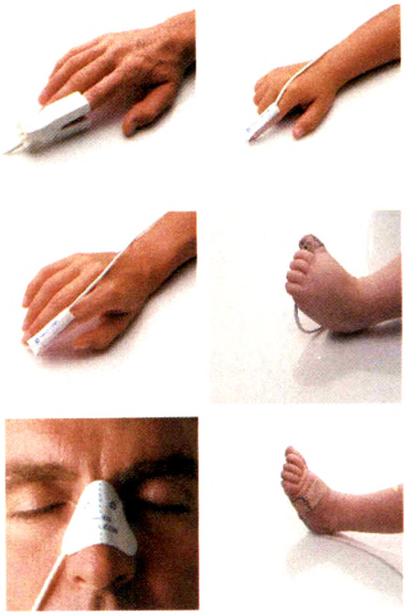
With each heartbeat, there is real-time, non-invasive measurement of arterial oxygen saturation, pulse rate, and pulse amplitude... Information that is critical to your patient's well-being.

**Variable beep plus an alarm system for early warning and instant detection.**

The unique variable beep warns instantly if the patient's oxygen level changes. So corrective action can be taken immediately... before complications develop.

Plus, audible and visual alarms alert if saturation or pulse rate fall outside preset limits.

An unprecedented safety net.



**A complete family of sensors for a wide range of non-invasive oxygen monitoring needs.**

You can choose sensors in different sizes and configurations to monitor all patients—from neonates to adults.

Even in difficult cases such as low peripheral perfusion, active patients, and long-term care.

**Easy to use.**

Apply the sensor, switch on the monitor, and read the results.

There's no site preparation, no heater, and no need to move the sensor frequently.

For more information, write or call Nellcor toll-free at 800 433-1244. (In California, 800 351-9754)

The Nellcor N-100 pulse oximeter. Setting the standard in hypoxemia monitoring.

NELLCOR®

Nellcor Incorporated
25495 Whitesell Street
Hayward, California 94545
415 887-5858
Telex 172 428

*Bibliography on file at Nellcor Incorporated.

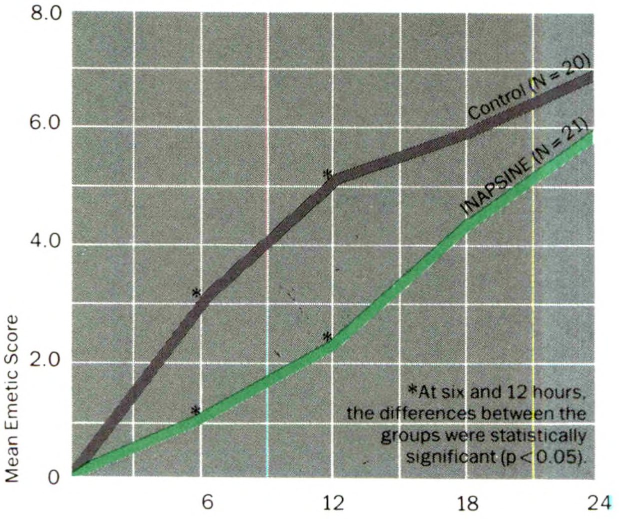
Nellcor is a registered trademark of Nellcor Incorporated.

## 1974:

“…we found droperidol [INAPSINE®] to be a safe and effective prophylactic anti-emetic agent in this group of patients at high emetic risk.”①

Double-blind study of 41 patients undergoing hysterectomy. Twenty-one patients received 5 mg INAPSINE shortly after surgery began, while 20 patients received placebo. Postoperative emesis was rated according to an emetic scoring system. Patients receiving INAPSINE had significantly less frequent and less severe nausea, retching and vomiting during the first 12 postoperative hours.

*INAPSINE vs placebo: mean total emetic scores. The lower the score, the fewer and less severe the incidents of emesis. (Adapted from Patton CM Jr, Moon MR, Dannemiller FJ¹)*

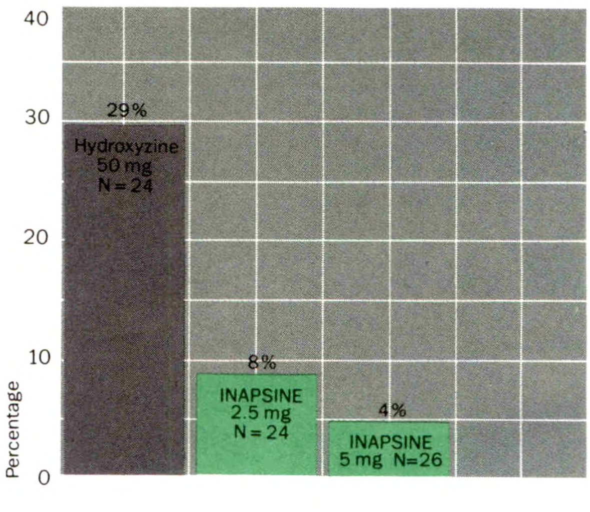


## 1984:

“The incidence of postoperative nausea/vomiting…was higher in patients who received hydroxyzine as premedicant compared to those who received droperidol [INAPSINE] ($p < 0.05$).”②

Double-blind comparison of INAPSINE 5 mg, INAPSINE 2.5 mg and hydroxyzine 50 mg, combined with meperidine or morphine and glycopyrrolate, as premedication in 74 women undergoing major elective gynecologic surgery. Significantly fewer of the patients receiving INAPSINE experienced postoperative nausea/vomiting than those receiving hydroxyzine ($p < 0.05$).

*Percentage of patients experiencing postoperative nausea/vomiting according to premedication ($p < 0.05$). (Based on Mehta P, Theriot E, Mehrotra D, et al²)*



Before prescribing please consult complete prescribing information, of which the following is a brief summary.
Protect from light. Store at room temperature.
FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY.
Droperidol is a neuroleptic (tranquilizer) agent.
**DESCRIPTION:** *2 ml. and 5 ml. ampoules:* Each ml. contains Droperidol 2.5 mg. and lactic acid for pH adjustment to 3.4 ± 0.4 *0 ml. Vials:* Each ml. contains Droperidol 2.5 mg. with 1.8 mg. methylparaben and 0.2 mg. propylparaben, and lactic acid for pH adjustment to 3.4 ± 0.4
**INDICATIONS:** INAPSINE (droperidol) is indicated: • to produce tranquilization and to reduce the incidence of nausea and vomiting in surgical and diagnostic procedures; • for premedication, induction, and as an adjunct in the maintenance of general and regional anesthesia; • in neuroleptanalgesia in which INAPSINE (droperidol) is given concurrently with a narcotic analgesic, such as SUBLIMAZE® (fentanyl) injection, to aid in producing tranquility and decreasing anxiety and pain.
**CONTRAINDICATIONS:** INAPSINE (droperidol) is contraindicated in patients with known intolerance to the drug.
**WARNINGS:** FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD BE READILY AVAILABLE.
As with other CNS depressant drugs, patients who have received INAPSINE (droperidol) should have appropriate surveillance.

If INAPSINE (droperidol) is administered with a narcotic analgesic such as SUBLIMAZE (fentanyl), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used, resuscitative equipment and a narcotic antagonist should be readily available to manage apnea. See package insert for fentanyl before using. Narcotic analgesics such as SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once this effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INAPSINE (droperidol), the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses as low as ¼ to ⅓ those usually recommended.

**PRECAUTIONS:** The initial dose of INAPSINE (droperidol) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses. Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms, INAPSINE (droperidol) can also alter circulation. Therefore, when INAPSINE (droperidol) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.

If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should also be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE (droperidol) due to the alpha-adrenergic blocking action of droperidol.

Since INAPSINE (droperidol) may decrease pulmonary arterial pressure, this fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. Vital signs should be monitored routinely.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effect with INAPSINE (droperidol). When patients have received such drugs, the dose of INAPSINE (droperidol) required will be less than usual. Likewise, following the administration of INAPSINE (droperidol), the dose of other CNS depressant drugs should be reduced.

INAPSINE (droperidol) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

When the EEG is used for postoperative monitoring, it may be

# Documenting a Decade of Significantly Superior Antiemetic Protection

**Early Prophylaxis for Postoperative Nausea and Vomiting**

# Inapsine®

## (droperidol) Injection

The Premedication That Does More Than Premedicate

References:

① Patton CM Jr, Moon MR, Dannemiller FJ: The prophylactic antiemetic effect of droperidol. *Anesth Analg* 1974;53:361-364.

② Mehta P, Theriot E, Mehrotra D, et al: Comparative evaluation of preanesthetic medications. *Cur Ther Res* 1984;35:715-720.

found that the EEG pattern returns to normal slowly.

Since INAPSINE (droperidol) is frequently used with the narcotic analgesic SUBLIMAZE (fentanyl), it should be noted that fentanyl may produce bradycardia, which may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias. (See full prescribing information for complete description.)

**ADVERSE REACTION:** The most common adverse reactions reported to occur with INAPSINE (droperidol) are mild to moderate hypotension and occasionally tachycardia, but these effects usually subside without treatment. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Postoperative drowsiness is also frequently reported.

Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of INAPSINE (droperidol). Restlessness, hyperactivity, and anxiety which can be either the result of inadequate dosage of INAPSINE (droperidol) or a part of the symptom complex of akathisia may occur. When extrapyramidal symptoms occur, they can usually be controlled with anti-parkinson agents.

Other adverse reactions that have been reported are dizziness, chills and/or shivering, laryngospasm, bronchospasm and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression).

When INAPSINE (droperidol) is used with a narcotic analgesic such as SUBLIMAZE (fentanyl), respiratory depression, apnea, and muscular rigidity can occur; if these remain untreated, respiratory arrest could occur.

Elevated blood pressure, with or without pre-existing hypertension, has been reported following administration of INAPSINE (droperidol) combined with SUBLIMAZE (fentanyl) or other parenteral analgesics. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

**DOSAGE AND ADMINISTRATION:** Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

**Usual Adult Dosage**

I. Premedication—(to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs) 2.5 to 10 mg. (1 to 4 ml.) may be administered intramuscularly 30 to 60 minutes preoperatively.

II. Adjunct to General Anesthesia
Induction—2.5 mg. (1 ml.) per 20 to 25 pounds may be administered (usually intravenously) along with an analgesic and/or general anesthetic. Smaller doses may be adequate. The total amount of INAPSINE (droperidol) administered should be titrated to obtain the desired effect based on the individual patient's response.
Maintenance—1.25 to 2.5 mg. (0.5 to 1 ml.) usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).

If INNOVAR® injection is administered in addition to INAPSI (droperidol), the calculation of the recommended dose of INAPSINE (droperidol) should include the droperidol containe in the INNOVAR injection. See INNOVAR injection Package Ins for full prescribing information.

III. Use Without A General Anesthetic In Diagnostic Procedures—Administer the usual I.M. premedication 2.5 to 10 mg. (1 to 4 30 to 60 minutes before the procedure. Additional 1.25 to 2.5 mg. (0.5 to 1 ml.) amounts of INAPSINE (droperidol) may be administered, usually intravenously (see warning regarding u with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).

Note: When INAPSINE (droperidol) is used in certain procedures, such as bronchoscopy, appropriate topical anesthesia still necessary.

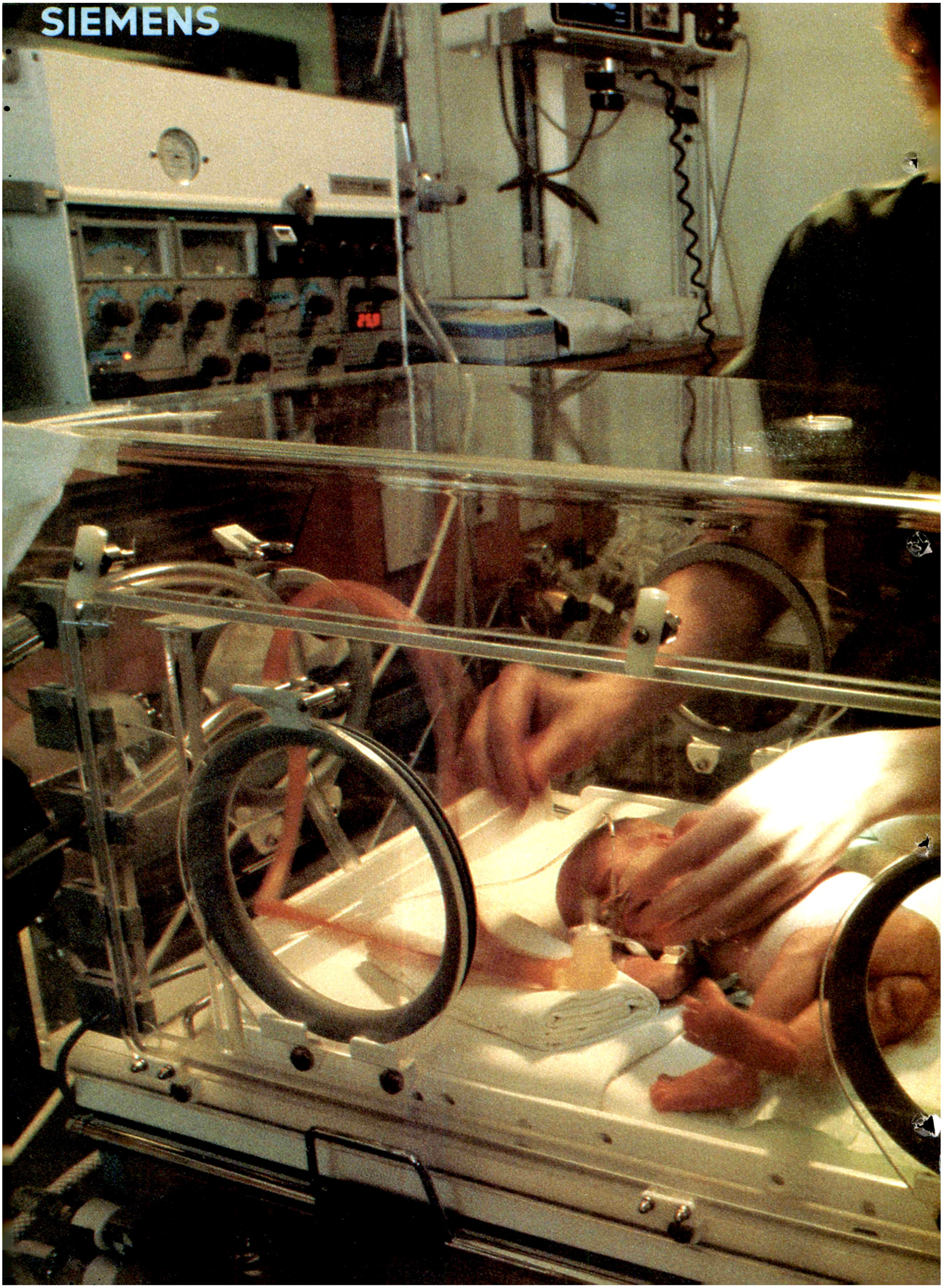
IV. Adjunct to Regional Anesthesia—2.5 to 5 mg. (1 to 2 ml.) may be administered intramuscularly or slowly intravenously whe additional sedation is required.

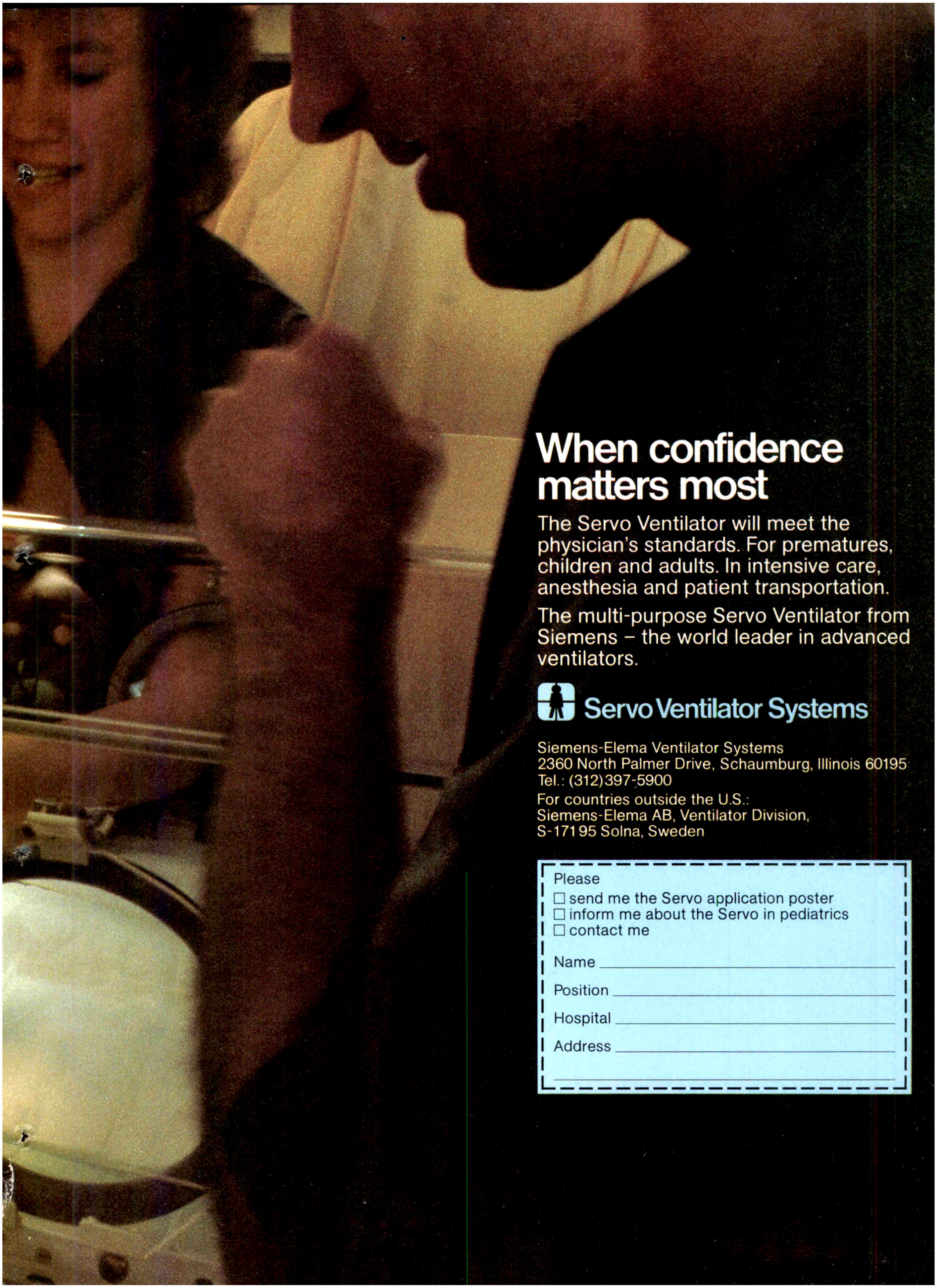
**How Supplied:** *2 ml. and 5 ml. ampoules*—packages of 10; *10 ml. multiple-dose vials*—packages of 10.
U.S. Patent No. 3,161,645
NDC 50458-010-02; NDC 50458-010-05; NDC 50458-010-10
March 1980, Revised June 1980 IP41C98-M
Manufactured by TAYLOR PHARMACAL CO. for

JANSSEN
PHARMACEUTICA

Janssen Pharmaceutica Inc.
Piscataway, New Jersey 088

© Janssen Pharmaceutica Inc. 1985 JPI-597 R


SIEMENS



## When confidence matters most

The Servo Ventilator will meet the physician's standards. For prematures, children and adults. In intensive care, anesthesia and patient transportation.

The multi-purpose Servo Ventilator from Siemens – the world leader in advanced ventilators.

**Servo Ventilator Systems**

Siemens-Elema Ventilator Systems
2360 North Palmer Drive, Schaumburg, Illinois 60195
Tel.: (312) 397-5900

For countries outside the U.S.:
Siemens-Elema AB, Ventilator Division,
S-171 95 Solna, Sweden

Please
☐ send me the Servo application poster
☐ inform me about the Servo in pediatrics
☐ contact me

Name ______________________________

Position ______________________________

Hospital ______________________________

Address ______________________________

______________________________

# INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

## THE B.B. SANKEY IARS ANESTHESIA ADVANCEMENT AWARD

The B.B. Sankey Anesthesia Advancement Award has been established to expand upon and replace the IARS Research Award. This new award is intended to foster investigative efforts in the fields of anesthesia research, clinical care, education and administration.

The recipients of the 1985 Sankey Anesthesia Advancement Awards are:

Roger S. Brett, MD, PhD, State University of New York, Stony Brook, New York
Patrick Curling, MD, Emory University School of Medicine, Atlanta, Georgia
Richard F. Davis, MD, University of Florida College of Medicine, Gainesville, Florida

## 1986 B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

Applications for up to $25,000 are invited for the 1986 Award, subject to the following basic conditions:

- The proposal must be within the general field of anesthesiology and may be for research, clinical care, education or administration.
- The applicant must be a member of the International Anesthesia Research Society.
- Applications must be received in the IARS Cleveland office not later than December 16, 1985.
- The official application form for the award must be used. This form, as well as the guidelines for applicants, is available on request to:

Emerson A. Moffitt, MD
Executive Secretary
International Anesthesia Research Society
3645 Warrensville Center Road
Cleveland, Ohio 44122, USA
Telephone: (216) 295-1124

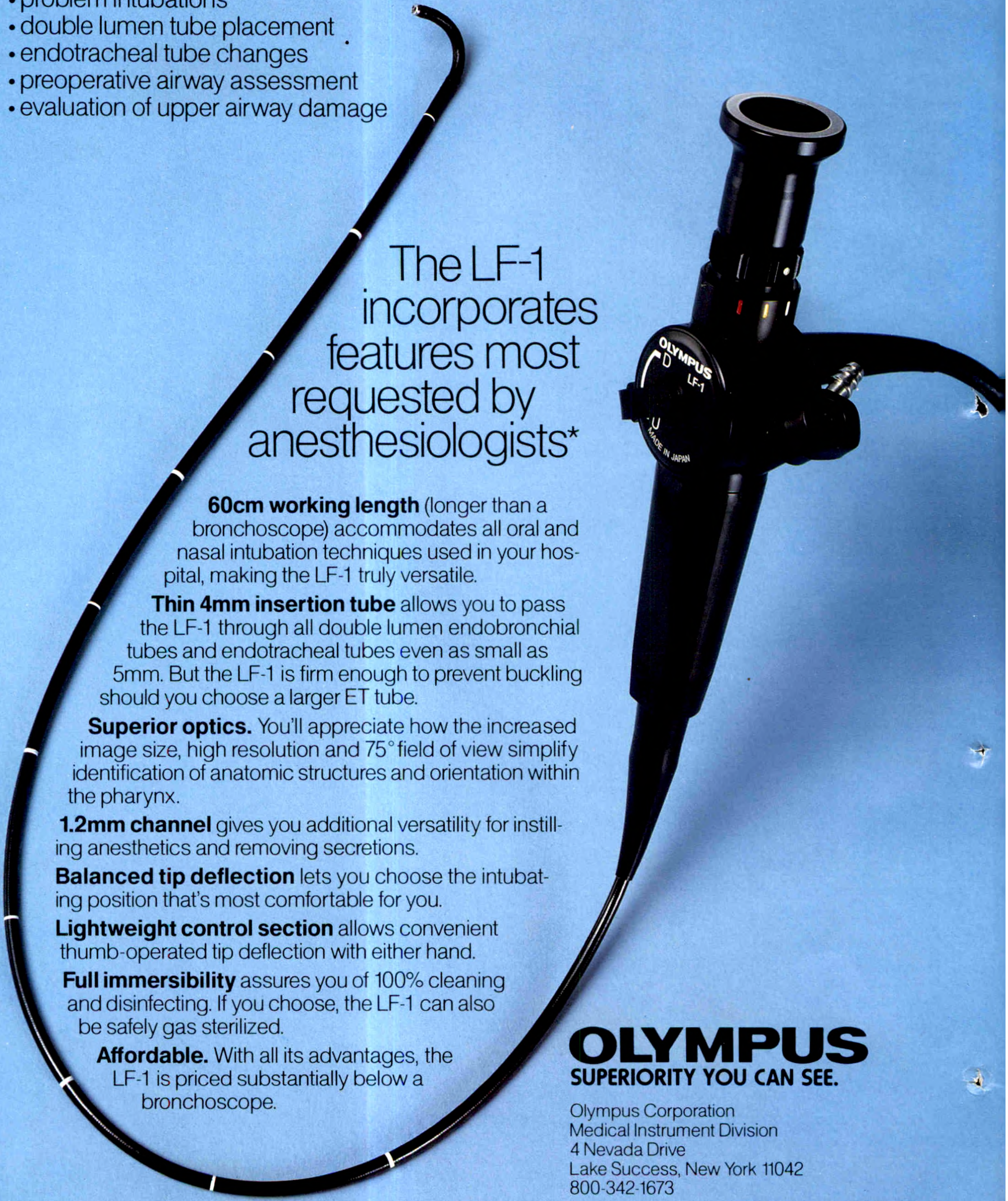
The 1986 Award(s) will be announced at the Annual Meeting (60th Congress) of the International Anesthesia Research Society to be held at Caesars Palace, Las Vegas, Nevada, March 15–19, 1986.

# Introducing the only fiberscope designed for the anesthesiologist.

## Olympus LF-1

P 24582

**OLYMPUS**
SUPERIORITY YOU CAN SEE.



# The Olympus LF-1 Intubation Scope designed specifically for:

- problem intubations
- double lumen tube placement
- endotracheal tube changes
- preoperative airway assessment
- evaluation of upper airway damage

## The LF-1 incorporates features most requested by anesthesiologists*

**60cm working length** (longer than a bronchoscope) accommodates all oral and nasal intubation techniques used in your hospital, making the LF-1 truly versatile.

**Thin 4mm insertion tube** allows you to pass the LF-1 through all double lumen endobronchial tubes and endotracheal tubes even as small as 5mm. But the LF-1 is firm enough to prevent buckling should you choose a larger ET tube.

**Superior optics.** You'll appreciate how the increased image size, high resolution and 75° field of view simplify identification of anatomic structures and orientation within the pharynx.

**1.2mm channel** gives you additional versatility for instilling anesthetics and removing secretions.

**Balanced tip deflection** lets you choose the intubating position that's most comfortable for you.

**Lightweight control section** allows convenient thumb-operated tip deflection with either hand.

**Full immersibility** assures you of 100% cleaning and disinfecting. If you choose, the LF-1 can also be safely gas sterilized.

**Affordable.** With all its advantages, the LF-1 is priced substantially below a bronchoscope.

**OLYMPUS**
**SUPERIORITY YOU CAN SEE.**

Olympus Corporation
Medical Instrument Division
4 Nevada Drive
Lake Success, New York 11042
800-342-1673

*From a market survey conducted by Olympus Corporation in January, 1983.

©1985 Olympus Corporation

**Introducing STRAPEZE™**

While others slip and slide all over the place, we've made a name for ourselves by staying put.

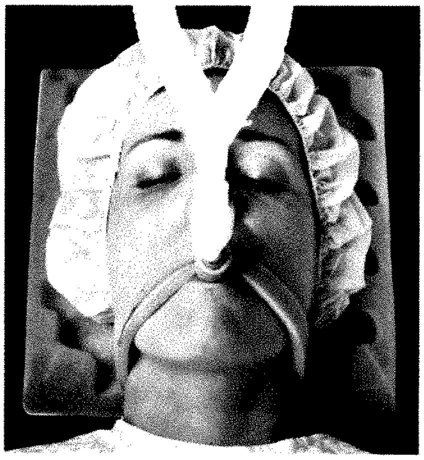
**No more fumbling for the tape. No more sticky adhesive devices. And no more concerns for the security and safety of your patient's airway. Now enjoy the speed, simplicity and protection of STRAPEZE.**

**Strap versus tape**

Tape kinks, binds, and often loses its adhesive qualities under operating conditions. STRAPEZE, as its name implies, is a strap made of 100% non-allergenic Velfoam II®, a very durable and lightweight material with a foam core sandwiched between outer layers of soft, synthetic lambs-wool.

**So easy to apply**

The STRAPEZE "one-step" fastening concept brings a new measure of assurance and security to endotracheal tube placement. And there's nothing else like it for ease of use. You simply attach one end of STRAPEZE to the tube, slip the strap behind the patient's neck, loop around tube and fasten with the Velcro tab back onto the strap's velvety surface. Job finished!



**Stays put—or it's not STRAPEZE!**

Now you can forget about accidental extubations or bronchial intubations. STRAPEZE ensures precise and positive positioning of the tube. Where you put it, is where it stays. Which means the tube won't pull out, and it won't push down. Needless to say, such assurances can be a lifesaver.

**Another quality product from ProTechPacific**

STRAPEZE was designed to answer the demanding needs of today's medical professional. Its innovative simplicity erases the tedium and uncertainty of performing an important task. And its specialized function is another example of ProTech Pacific's ongoing commitment to your profession. STRAPEZE. New convenience. New security. New comfort. And, for all these assurances, very inexpensive. For the comfort of the intubated patient, STRAPEZE is here to stay. Because it *stays put*.

*U.S. Patents pending*

**ProTechPacific**

*1221 Andersen Drive*
*San Rafael, California 94901*
*Call Toll Free: 800/227-0517*
*In Calif. 415/459-0745*

*Manufacturers of Protective Medical Products*

# THROUGHOUT THE PERI-

## to relieve excessive anxiety

### Rapid relief of anxiety and apprehension

Anxiety is an extremely common reaction to the stress of anesthesia and surgery. Often at its most acute stage in the minutes just before induction, anxiety may even affect the outcome of the surgical procedure.[1]

To relieve anxiety promptly and predictably, no agent is more effective than Injectable Valium® (diazepam/Roche) I.V.

Within minutes after an I.V. injection,[2,3] most patients become noticeably calmer, sedated yet easily aroused if necessary. This response is prompt and predictable—just the kind you want in the anxious moments before surgery.

**Rarely compromises cardiac or respiratory function** Injectable Valium rarely produces clinically significant alterations in basal circulatory parameters.[4-6] In a series of 16,000 patients, apnea occurred in only three patients given Injectable Valium intravenously.[7] However, caution should be taken when administering the agent to elderly or debilitated patients with limited pulmonary reserve. Resuscitative equipment should be available for all patients, and narcotics should be reduced by one-third or more; in some cases they may be eliminated.

Copyright © 1985
by Roche Products Inc.
All rights reserved.

# OPERATIVE PERIOD

## to diminish recall

**Diminishes recall of unpleasant or painful procedures** When patients have vivid memories of invasive procedures, they may be less than willing to undergo such procedures again, even if they are medically necessary.[8,9] Recall of procedures such as endotracheal intubation can be diminished by the rapid-acting amnesic effect of Injectable Valium (diazepam/Roche) I.V. Anterograde amnesia usually begins within three minutes after a single I.V. injection, peaks within ten minutes and lasts for 20 to 60 minutes.[3,10,11]

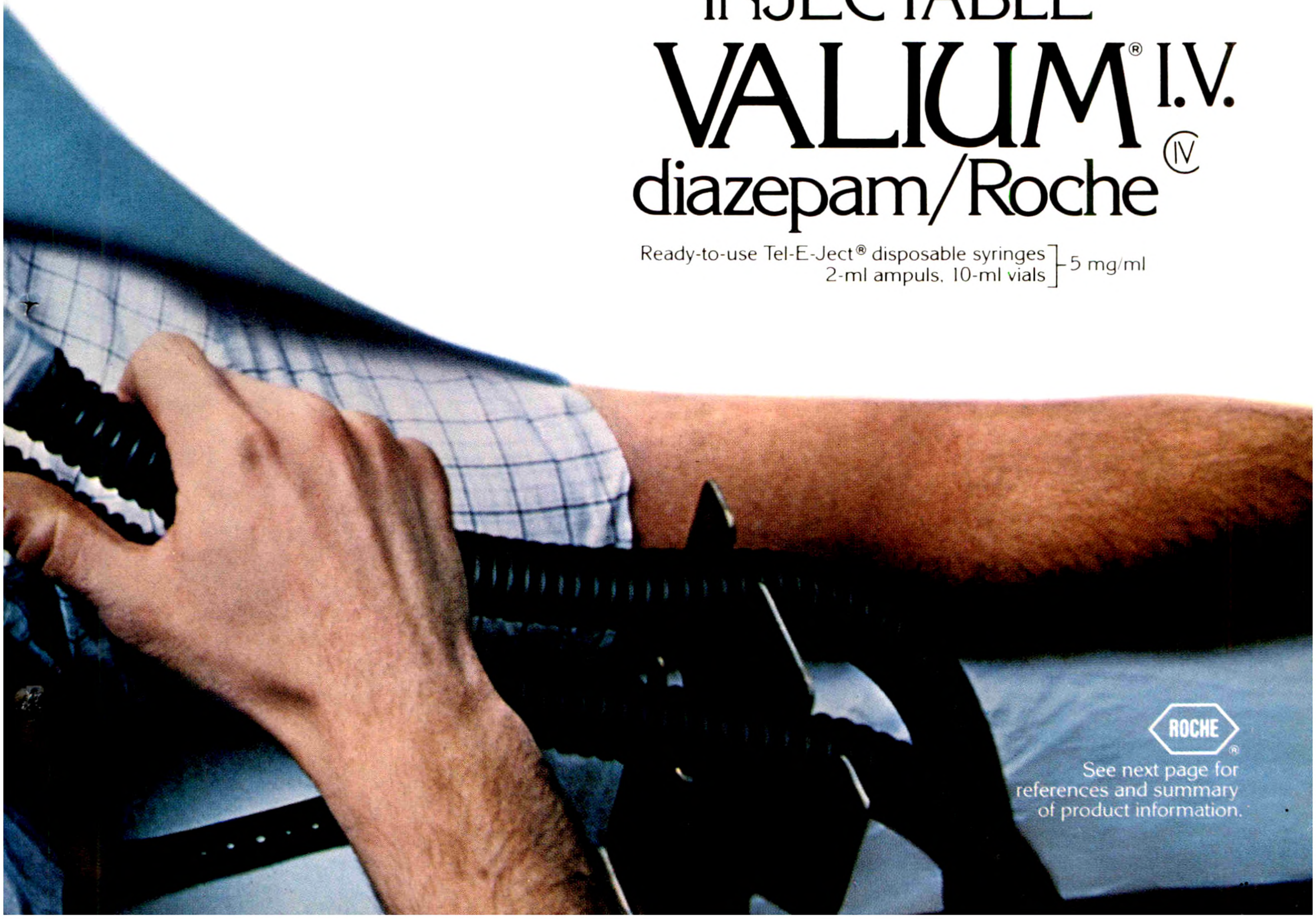
This predictable pattern of action distinguishes Injectable Valium from other agents that can produce amnesia and sedation. Other agents can take 15 to 30 minutes to achieve the desired effect, and the effects may last for 24 hours or more.[2] However, patients should be warned about driving or performing other potentially dangerous activities after receiving Injectable Valium.

**Easily titrated for desired effect** The compact 10-mg prefilled syringe makes individualized titration of Injectable Valium (diazepam/Roche) simple because there is convenient, easily readable milligram calibration on both sides of the barrel. And unlike other injectable agents, Injectable Valium needs no reconstitution before administration and no refrigeration during storage. Do not mix or dilute Valium with other drugs or solutions. Administer slowly in a large vein or through the infusion line as close to the vein insertion site as possible.

Injectable Valium. In a class by itself for rapidly relieving anxiety and diminishing recall.

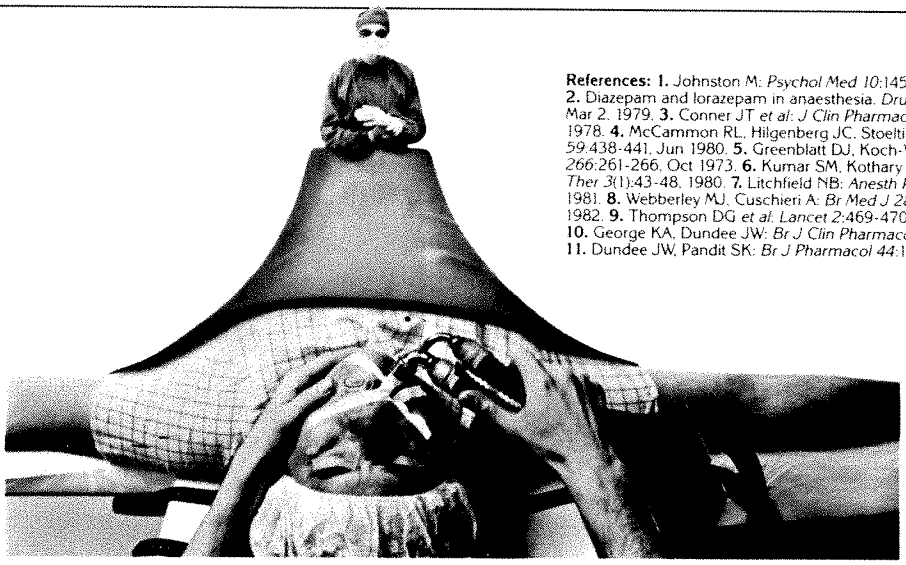
Prompt
Predictable
INJECTABLE
VALIUM® I.V. Ⓘⓥ
diazepam/Roche

Ready-to-use Tel-E-Ject® disposable syringes } 5 mg/ml
2-ml ampuls, 10-ml vials }



ROCHE®

See next page for references and summary of product information.



**References: 1.** Johnston M: *Psychol Med 10*:145-152, Feb 1980. **2.** Diazepam and lorazepam in anaesthesia. *Drug Ther Bull 17*:19-20, Mar 2, 1979. **3.** Conner JT *et al*: *J Clin Pharmacol 18*:285-292, May-Jun 1978. **4.** McCammon RL, Hilgenberg JC, Stoelting RK: *Anesth Analg 59*:438-441, Jun 1980. **5.** Greenblatt DJ, Koch-Weser J: *Am J Med Sci 266*:261-266, Oct 1973. **6.** Kumar SM, Kothary SP, Zsigmond EK: *Clin Ther 3*(1):43-48, 1980. **7.** Litchfield NB: *Anesth Prog 29*:11-17, Jan-Feb, 1981. **8.** Webberley MJ, Cuschieri A: *Br Med J 285*:251-252, Jul 24, 1982. **9.** Thompson DG *et al*: *Lancet 2*:469-470, Aug 30, 1980. **10.** George KA, Dundee JW: *Br J Clin Pharmacol 4*:45-50, Feb 1977. **11.** Dundee JW, Pandit SK: *Br J Pharmacol 44*:140-144, Jan 1972.

# INJECTABLE VALIUM® (diazepam/Roche) CIV

**Please consult complete product information, a summary of which follows:**

**Indications:** Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; tetanus; status epilepticus, severe recurrent seizures; adjunctively in anxiety, tension or acute stress reactions prior to endoscopic/surgical procedures; cardioversion.

**Contraindications:** Hypersensitivity; acute narrow angle glaucoma; may be used in patients with open angle glaucoma receiving appropriate therapy.

**Warnings:** *To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling and, rarely, vascular impairment when used I.V.: inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins,* i.e., *dorsum of hand or wrist; use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*

Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea; have resuscitative facilities available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least 1/3, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status.

Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation after long use of excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after long, continuous use at high therapeutic levels. After extended therapy, gradually taper dosage.

> *Usage in Pregnancy:* **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations, as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for OB use.

Efficacy/safety not established in neonates (age 30 days or less); prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence; can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.

**Precautions:** Although promptly controlled, seizures may return; readminister if necessary; not recommended for long-term maintenance therapy.

If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam/Roche), *i.e.*, phenothiazines, narcotics, barbiturates, MAO inhibitors, antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

**Adverse Reactions:** Drowsiness, fatigue, ataxia, venous thrombosis/phlebitis at injection site, confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo, constipation, nausea, incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat and chest have been reported in peroral endoscopic procedures. Isolated reports of neutropenia, jaundice; periodic blood counts, liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

**Dosage:** Usual initial dose in older children and adults is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.)

For dosages in infants and children see below; have resuscitative facilities available.

*I.M. use: by deep injection into the muscle.*

*I.V. use: inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins,* i.e., *dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*

Moderate anxiety disorders and symptoms of anxiety, 2 to 5 mg I.M. or I.V. and severe anxiety disorders and symptoms of anxiety, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcohol withdrawal, 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary. Muscle spasm, in adults, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses): in children, *administer I.V. slowly;* for tetanus in infants over 30 days of age, 1 to 2 mg I.M. or I.V., repeat every 3 to 4 hours if necessary; in children 5 years or older, 5 to 10 mg repeated every 3 to 4 hours as needed. Respiratory assistance should be available.

Status epilepticus, severe recurrent convulsive seizures (I.V. route preferred), 5 to 10 mg adult dose administered slowly, repeat at 10- to 15-minute intervals up to 30 mg maximum. Repeat in 2 to 4 hours if necessary, keeping in mind possibility of residual active metabolites. Use caution in presence of chronic lung disease or unstable cardiovascular status. Infants (over 30 days) and children (under 5 years), 0.2 to 0.5 mg slowly every 2 to 5 min., up to 5 mg (I.V. preferred). Children 5 years plus, 1 mg every 2 to 5 min., up to 10 mg (slow I.V. preferred); repeat in 2 to 4 hours if needed. EEG monitoring may be helpful.

In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg I.V. within 5 to 10 minutes prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

**Management of Overdosage:** Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of limited value.

**Supplied:** Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1 and 10; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

ROCHE®

Manufactured by Hoffmann-La Roche Inc.
Nutley, New Jersey 07110
Distributed by Roche Products Inc.
Manati, Puerto Rico 00701

For the Special Health Care Needs and Concerns of Youth...

Journal of Adolescent Health Care

OFFICIAL PUBLICATION OF THE SOCIETY FOR ADOLESCENT MEDICINE

Editor-in-Chief: **H. Verdain Barnes, M.D.**
Wright State University School of Medicine, Dayton, Ohio

The comprehensive nature and outstanding scientific quality of the **Journal of Adolescent Health Care** have established it as the leading publication in its field – and a necessary resource for pediatricians, family practitioners, internists, psychologists, sociologists, and all other professionals involved in improving the quality of adolescent health care.

Now in its fifth successful year, and edited by leading authorities, this interdisciplinary journal is devoted to developing effective responses to the acute and chronic health care problems of the adolescent. Publication of the latest scientific results keeps the reader abreast of the newest developments in this rapidly expanding specialty.

Every issue contains original articles, analytic subject reviews, and case reports, as well as a special section featuring a bibliography of recent articles in related disciplines.

1985 Subscription Information
Volume 6 (6 issues) ISSN 0197-0070

| | |
|---|---|
| Institutional rate | $110.00 |
| Personal rate | $70.00 |
| Intern/Resident rate | $44.00 |

For sample copies, send to

**in North and South America:**
Elsevier Science Publishing Co., Inc.
P.O. Box 1663
Grand Central Station
New York, NY 10163

**in the rest of the world:**
Elsevier Science Publishers
Direct Mail Department
P.O. Box 211
1000 AE Amsterdam
The Netherlands

For air delivery in the U.S., Canada, and Mexico, add $15.00. Subscribers outside the U.S. should add: $12.00 for surface delivery (not available to Europe); $14.50 for surface air lift to Europe; $36.00 for air delivery to the rest of the world; or $22.00 for delivery to Japan (via surface air lift only).

**Note: Send subscription orders either to your usual supplier or to the New York address.**

Subscriptions begin with the first issue of the calendar year.
Subscription rates valid until December 31, 1985.
Orders from non-U.S. customers must be prepaid.

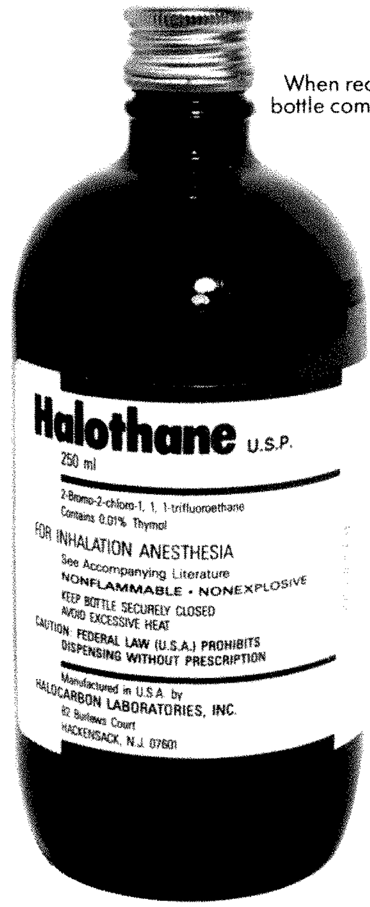
Note: Publisher will honor Intern/Resident status for a maximum of three years; the Intern/Resident rate is subject to increase annually.

EB 325

ELSEVIER

HALOTHANE U.S.P.

Produced by
Halocarbon Laboratories, Inc.


Halothane U.S.P.
250 ml
2-Bromo-2-chloro-1, 1, 1-trifluoroethane
Contains 0.01% Thymol
FOR INHALATION ANESTHESIA
See Accompanying Literature
NONFLAMMABLE · NONEXPLOSIVE
KEEP BOTTLE SECURELY CLOSED
AVOID EXCESSIVE HEAT
CAUTION: FEDERAL LAW (U.S.A.) PROHIBITS DISPENSING WITHOUT PRESCRIPTION
Manufactured in U.S.A. by
HALOCARBON LABORATORIES, INC.
82 Burlews Court
HACKENSACK, N.J. 07601

When requested bottle comes with collar.

- First Maker of Fluorinated Anesthetics in the U.S.A.
- Pioneer in Anesthetic Purity
- Lowest Price of Any Potent Anesthetic

HALOCARBON
LABORATORIES, INC.
P.O. Box 833
Hackensack, NJ 07602
(201) 343-8703

# The only constant in critical care medicine is change.

In critical care medicine, change is everywhere, and constant. Technologies change. Therapies change. Even economic relationships change, as witnessed by DRGs and their far reaching effects. It is evident that those who practice in the field of critical care, and those who supply the tools they need, must be alert to change, and have the capacity to deal with it.

Bard Critical Care is a company formed and shaped by change. It is also a company we hope you will come to consider a constant—a reliable supplier of some of your most important medical equipment.

Created by the merger of Bard Biomedical and USCI Critical Care, our new structure puts us in a much better position to offer you the products, services, and ideas you constantly require in your chosen field.

# Only change keeps a company constant.

## Introducing Bard Critical Care.

Whether it's an improved ECG electrode…better therapy through AV Sequential Temporary Pacing…a more logically designed thermodilution catheter…the sound technology of Hemaquet™ catheter introducers…or a thrombo-resistant umbilical catheter…you can be certain that Bard Critical Care will remain in the forefront of change, and that you and your patients will constantly benefit from it.

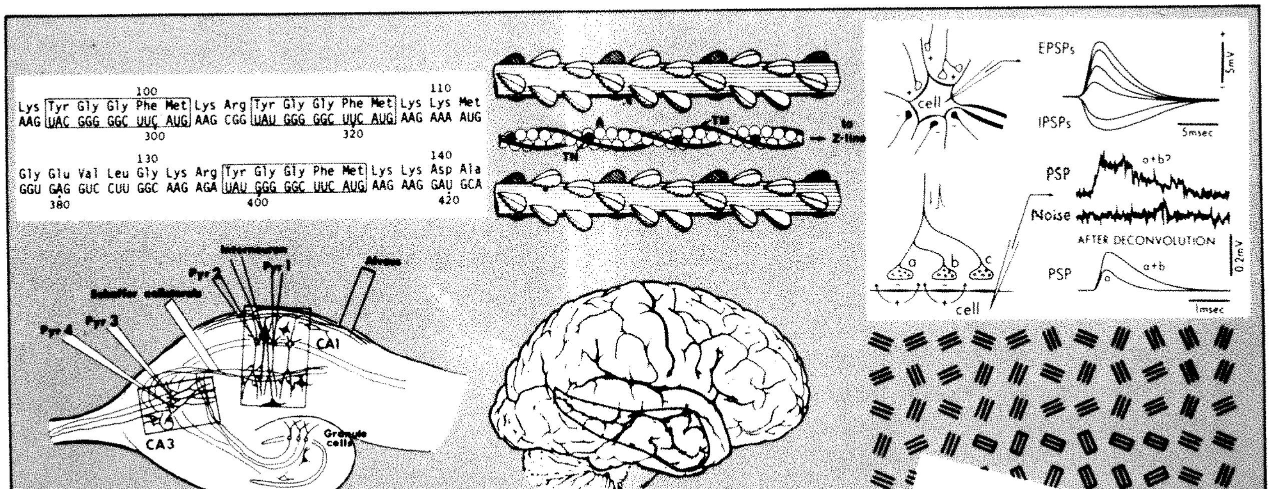
Only by knowing how to change, and how to respond to it, can Bard Critical Care become what we intend to be: a supplier you will regard as one of your constants for many years to come.

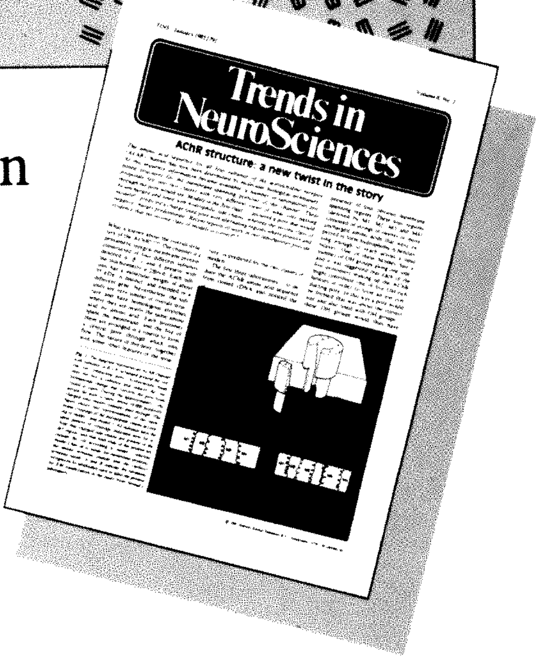
BARD

**Bard Critical Care Division**
C.R. Bard, Inc., P.O. Box 7000, 129 Concord Rd., Billerica, Mass. 01821

Toll-free telephone: 1-800-323-3419
In Massachusetts, Alaska, and Hawaii: 617-667-8810

# Trends in NeuroSciences


100
110
Lys Tyr Gly Gly Phe Met Lys Arg Tyr Gly Gly Phe Met Lys Lys Met
AAG UAC GGG GGC UUC AUG AAG CGG UAU GGG GGC UUC AUG AAG AAA AUG
300
320
130
140
Gly Glu Val Leu Gly Lys Arg Tyr Gly Gly Phe Met Lys Lys Asp Ala
GGU GAG GUC CUU GGC AAG AGA UAU GGG GGC UUC AUG AAG AAG GAU GCA
380
400
420
Z-line
Interneuron
Pyr 1
Pyr 2
Pyr 3
Pyr 4
Alveus
Schaffer collaterals
CA1
CA3
Granule cells
cell
EPSPs
IPSPs
5mV
5msec
PSP
Noise
AFTER DECONVOLUTION
0.2mV
1msec
a
b
c
a+b
a+b?


Trends in NeuroSciences

AChR structure: a new twist in the story

## From genes to behaviour –the central connection

This is probably the most exciting time to be working in neuroscience. At last it seems as though many of the secrets of the nervous system are yielding to research. The genes for the acetylcholine receptor, the sodium channel and the three opioid peptide precursors have all been cloned. The crucial role of molecular genetics within neuroscience is firmly established.

The new technology has demonstrated the ability of a handful of gene products to orchestrate a complex sequence of behaviour in the marine mollusc *Aplysia*. Rapid progress is also being made in understanding how specific gene products control development in the insect's nervous system, or regulate the switching of transmitter production in adult mammalian neurons. Undoubtably molecular genetics will have a major impact on clinical neuroscience during the 1980s.

**SPECIAL DISCOUNT RATES**

**Special subscription rates are still available to all students (undergraduate, graduate, postgraduate etc). The discount rates are also applicable to neurology residents in North America.**

Gene research in neuroscience is not the only area where activities are occuring at an explosive rate. PET studies of human cognitive function, computer monitoring of whole body and limb movement and psychophysical testing of perceptual activities are all contributing to our knowledge of higher brain functions in health and disease.

**Trends in NeuroSciences** is the only review journal which covers all aspects of neuroscience. Its unique style makes it accessible to researchers and students alike. Don't miss out on the excitement, subscribe to **Trends in NeuroSciences** today.

**Articles published in 1984 included:**

Localisation of the gene for Huntington's chorea *P. S. Harper*
Homoeotic gene transcripts in the neural tissues of insects *Matthew P. Scott*
Neuronal development in *Caenorhabditis elegans* by *Martin Chalfie*
The development of specific motor pathways in the chick embryo *Lynn Landmesser*
The psychology and physiology of colour vision *Nigel W. Daw*
The natural vocalizations of non-human primates *Robert M. Seyfarth and Dorothy L. Cheney*
Motor neuron diseases and amytrophic lateral sclerosis *Lewis P. Rowland*

**Subscription prices 1985**

A personal subscription to **Trends in NeuroSciences** comprises 12 issues and costs only £28.00 (UK), $49.00 (USA and Canada), Dfl. 130.00 (Europe), Dfl. 140.00 (Rest of the world). A library subscription comprises 12 issues plus an annual hard bound compendium for reference. This subscription costs Dfl. 430 (UK, USA, Canada and Europe) or Dfl. 445 (Rest of the world).

Payment must accompany personal subscriptions and may be made by cheque, made out to 'Elsevier' in pounds sterling or US dollars or by credit card. We accept AmEx, VISA and Access/Mastercard/Eurocard. Please supply card number, expiry date, issuing bank (if appropriate), the cardholder's name and address and signature.

Please send your subscription or request for a free sample copy to one of the addresses below.

Elsevier Publications (Cambridge)
68 Hills Road
Cambridge
CB2 1LA
UK

Elsevier Science Publishing Co Inc
52 Vanderbilt Avenue
New York
NY 10017
USA

Elsevier Science Publishers
Biomedical Division
PO Box 1527
1000AC Amsterdam
The Netherlands

# IARS MEMBERSHIP

## FOR YOUR IN-TRAINING AND CONTINUING MEDICAL EDUCATION

The International Anesthesia Research Society is a non-profit, scientific and educational corporation of the State of Ohio, founded in 1922 "to foster progress and research in anesthesia." To this end the Society

Publishes the oldest journal in the specialty, *Anesthesia and Analgesia*

Sponsors an annual scientific meeting (Congress) which is held in March each year

Funds anesthesia-related research through the IARS B.B. Sankey Anesthesia Advancement Award

Membership in the IARS is voluntary; it is also separate and distinct from membership in any other local, state, regional or national anesthesia organization or association. Membership is open to individuals who qualify in the various categories shown below; who complete the appropriate application and submit it to the IARS Cleveland office with the applicable dues. All memberships include a subscription to *Anesthesia and Analgesia*. Members and Associate Members are entitled to a reduced registration fee at the IARS annual meeting; Educational Members pay no registration fee.

## . . . . MEMBERSHIP CATEGORIES . . . .

**MEMBERSHIP:** Open to individuals with doctorate degrees, who are licensed to practice in the medical, osteopathic, dental or veterinary medicine fields (i.e., MD, MB, DO, DDS, DMD, DVM); and to individuals with doctorate degrees in any scientific discipline (PhD), who are engaged in academic, private or commercial research.

**ASSOCIATE MEMBERSHIP:** Open to individuals in the allied health professions, duly certified by their professional accrediting organization as nurse anesthetists (CRNA); respiratory therapists or technicians (RRT or CRTT); physician/anesthesia assistants (PA/MMS); and other allied health professionals in anesthesia-related practice.

*Annual Dues for Members and Associate Members:* $45.00 U.S.; $55.00 foreign. These memberships are entered on a calendar year basis only.

**EDUCATIONAL MEMBERSHIP:** Open (with certification by program director) to doctors (interns/residents) enrolled in anesthesiology training programs; nurses enrolled in nurse anesthesia schools; students enrolled in programs leading to certification as physician assistants, respiratory therapists or technicians

*Annual Dues for Educational Members:* One-half of member rate. These memberships are entered in January or July for 2, 3, or 4 year periods. Applications, certified by program directors, must accompany check to cover full membership period.

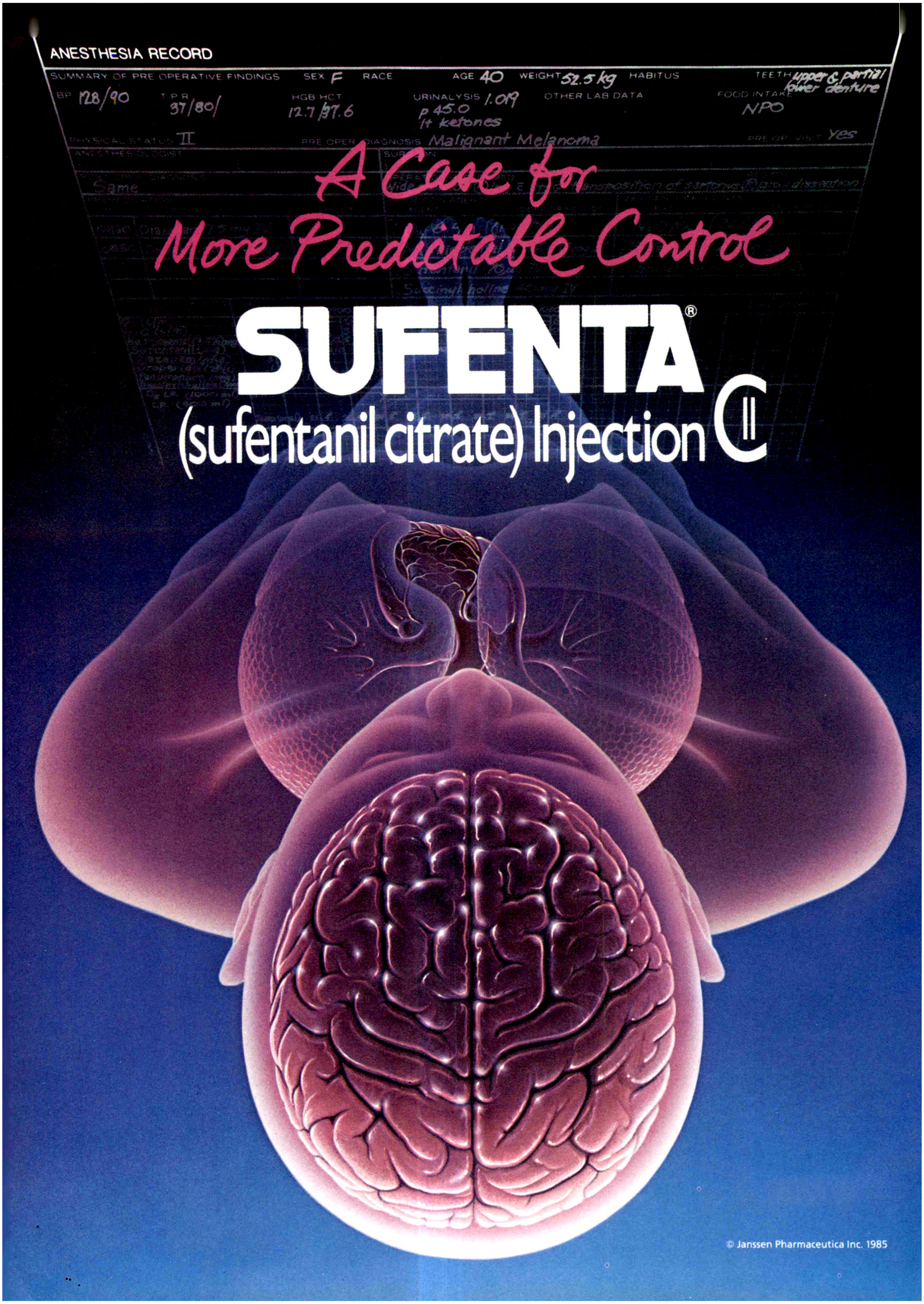
---

International Anesthesia Research Society
3645 Warrensville Center Road, Cleveland, Ohio 44122, USA

Please send me ______ application(s) for: Membership (______)
Associate Membership (______)
Educational Membership (______)

Please print clearly: ________________________________________
Name and Degree (MD, DO, CRNA, RN, RRT, etc.)

________________________________________________________________
Street Address                City, State, Zip Code (country)



ANESTHESIA RECORD

SUMMARY OF PRE OPERATIVE FINDINGS SEX F RACE AGE 40 WEIGHT 52.5 kg HABITUS TEETH upper & partial lower denture

BP 128/90 T P R 37/80/ HGB HCT 12.7/37.6 URINALYSIS 1.019 p 45.0 lt ketones OTHER LAB DATA FOOD INTAKE NPO

PHYSICAL STATUS II PRE OPER DIAGNOSIS Malignant Melanoma PRE OP VISIT Yes

© Janssen Pharmaceutica Inc. 1985

# ...More Predictable Control from Induction through Recovery

## COMPARED WITH ISOFLURANE*[1,2]

- Superior hemodynamic stability
- Shorter recovery times
- Better maintenance of postoperative analgesia
- Lower total cost per procedure

*In a comparative study[1,2] of patients undergoing major orthopedic surgery who received either SUFENTA-$N_2O$ (n=10) or isoflurane-$N_2O$ (n=10).

1. Scientific Exhibit, Sufentanil vs. Isoflurane in Major Orthopedic Procedures (Fahmy NR, Principal Investigator), March 1983.

2. Fahmy NR, Beemer GH, Roberts JT: Symposium Report, Advances in Anesthesia, a New Synthetic Narcotic for the 80s, Atlanta, Oct 8, 1983.

## COMPARED WITH FENTANYL[3,4]

- Smoother, more rapid induction
- When given before intubation, reduces hypertension and tachycardia
- Promotes fast, comfortable recovery
- More effective blocking of catecholamine response to surgery
- Superior intraoperative hemodynamic stability
- Smaller volume of injection
- Lower total cost per procedure

3. Smith NT, Dec-Silver H, Harrison WK, et al: ASA Abstract, Anesthesiology (Suppl) 57: A291, 1982.
4. Flacke JW, Bloor BC, Flacke WE, et al: Comparative Effects of Sufentanil and Fentanyl Versus Meperidine and Morphine in Balanced Anesthesia. Symposium Report, Advances in Anesthesia, a New Synthetic Narcotic for the 80s, Atlanta, Oct 8, 1983.

For full Prescribing Information, please see next page. JPI-514R

Announcing:
**Advances in Anesthesia**

New Janssen TELETOPICS™ Program...as close as your Touch-Tone® telephone...

To hear taped presentations, simply dial toll free 1-800-JANSSEN and listen for further instructions.

world leader in anesthesia research

**JANSSEN**
**PHARMACEUTICA**

# SUFENTA® (sufentanil citrate) Injection CII

**CAUTION:** Federal Law Prohibits Dispensing Without Prescription

## DESCRIPTION

SUFENTA (sufentanil citrate) is a potent opioid analgesic chemically designated as N-[4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1).

SUFENTA is a sterile, preservative-free, aqueous solution containing sufentanil citrate equivalent to 50 µg per ml of sufentanil base for intravenous injection. The solution has a pH range of 3.5-7.5

## CLINICAL PHARMACOLOGY

SUFENTA is an opioid analgesic. SUFENTA is approximately 5 to 7 times as potent as fentanyl (Dosage requirements for equianalgesic effect will be ⅕-⅐ those of fentanyl on a mg/kg basis.) At doses of up to 8 µg/kg, SUFENTA provides profound analgesia; at doses ≥8 µg/kg, SUFENTA produces a deep level of anesthesia. SUFENTA produces a dose related attenuation of catecholamine release, particularly norepinephrine.

The pharmacokinetics of SUFENTA can be described as a three-compartment model, with a distribution time of 0.72 minutes, redistribution of 13.7 minutes and an elimination half-life of 148 minutes. The liver and small intestine are the major sites of biotransformation. Approximately 80% of the administered dose is excreted within 24 hours and only 2% of the dose is eliminated as unchanged drug. Plasma protein binding of SUFENTA is approximately 92.5%.

SUFENTA has an immediate onset of action, with relatively limited accumulation. Rapid elimination from tissue storage sites allows for relatively more rapid recovery as compared with fentanyl. At dosages of SUFENTA of 1-2 µg/kg, recovery times are comparable to those observed with fentanyl; at dosages of >2-6 µg/kg, recovery times are comparable to enflurane, isoflurane and fentanyl. Within the anesthetic dosage range of 8-30 µg/kg of SUFENTA, recovery times are more rapid compared to equipotent fentanyl dosages.

At dosages of ≥8 µg/kg, SUFENTA produces hypnosis and anesthesia without the use of additional anesthetic agents. A deep level of anesthesia is maintained at these dosages, as demonstrated by EEG patterns. Dosages of up to 25 µg/kg attenuate the sympathetic response to surgical stress. The catecholamine response, particularly norepinephrine, is further attenuated at doses of SUFENTA of 25-30 µg/kg, with hemodynamic stability and preservation of favorable myocardial oxygen balance.

The vagolytic effects of pancuronium may produce a dose dependent elevation in heart rate during SUFENTA-oxygen anesthesia. The vagolytic effect of pancuronium may be reduced in patients administered nitrous oxide with SUFENTA. The use of moderate doses of pancuronium or of a less vagolytic neuromuscular blocking agent may be used to maintain a stable lower heart rate and blood pressure during SUFENTA-oxygen anesthesia.

Preliminary data suggest that in patients administered high doses of SUFENTA, initial dosage requirements for neuromuscular blocking agents are generally lower as compared to patients given fentanyl or halothane, and comparable to patients given enflurane.

Bradycardia is infrequently seen in patients administered SUFENTA-oxygen anesthesia. The use of nitrous oxide with high doses of SUFENTA may decrease mean arterial pressure, heart rate and cardiac output.

Assays of histamine in patients administered SUFENTA have shown no elevation in plasma histamine levels and no indication of histamine release.

SUFENTA at 20 µg/kg has been shown to provide more adequate reduction in intracranial volume than equivalent doses of fentanyl, based upon requirements for furosemide and anesthesia supplementation in one study of patients undergoing craniotomy. During carotid endarterectomy, SUFENTA produced EEG patterns and reductions in cerebral blood flow and oxygen utilization comparable to those of fentanyl.

The intraoperative use of SUFENTA at anesthetic dosages maintains cardiac output, with a slight reduction in systemic vascular resistance during the initial postoperative period. The incidence of postoperative hypertension, need for vasoactive agents and requirements for postoperative analgesics are generally reduced in patients administered moderate or high doses of SUFENTA as compared to patients given inhalation agents.

Decreased respiratory drive and increased airway resistance occur with SUFENTA. The duration and degree of respiratory depression are dose related when SUFENTA is used at sub-anesthetic dosages. At high doses, a pronounced decrease in pulmonary exchange and apnea may be produced.

## INDICATIONS AND USAGE

SUFENTA (sufentanil citrate) is indicated:

as an analgesic adjunct at dosages of up to 8 µg/kg in the maintenance of balanced general anesthesia.

as a primary anesthetic agent for the induction and maintenance of anesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, to provide favorable myocardial and cerebral oxygen balance or when extended postoperative ventilation is anticipated.

## CONTRAINDICATIONS

SUFENTA is contraindicated in patients with known hypersensitivity to the drug.

## WARNINGS

**SUFENTA should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.**

**An opioid antagonist, resuscitative and intubation equipment and oxygen should be readily available.**

SUFENTA may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence can be reduced by: 1) administration of up to ¼ of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA at dosages of up to 8 µg/kg, 2) administration of a full paralyzing dose of a neuromuscular blocking agent following loss of eyelash reflex when SUFENTA is used in anesthetic dosages (above 8 µg/kg) titrated by slow intravenous infusion, or, 3) simultaneous administration of SUFENTA and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA is used in rapidly administered anesthetic dosages (above 8 µg/kg).

The neuromuscular blocking agent used should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered anesthetic doses of SUFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

## PRECAUTIONS

The initial dose of SUFENTA should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses.

Vital signs should be monitored routinely.

Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA (see CLINICAL PHARMACOLOGY).

High doses of pancuronium may produce increases in heart rate during SUFENTA-oxygen anesthesia. Bradycardia has been reported infrequently with SUFENTA-oxygen anesthesia and has been responsive to atropine.

Head Injuries: SUFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: SUFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, SUFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA.

Drug Interactions: An additive effect with SUFENTA may be exhibited in patients receiving barbiturates, tranquilizers, other opioids, general anesthetics or other CNS depressants. In such cases of combined treatment, the dose of one or both agents should be reduced.

**Carcinogenesis, Mutagenesis and Impairment of Fertility:** No long-term animal studies of SUFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats revealed that single intravenous doses of SUFENTA as high as 80 µg/kg (approximately 2.5 times the upper human dose) produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity. See ANIMAL TOXICOLOGY for reproduction studies in rats and rabbits.

**Pregnancy Category C:** SUFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were most probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug.

No evidence of teratogenic effects have been observed after administration of SUFENTA in rats or rabbits.

There are no adequate and well-controlled studies in pregnant women. SUFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Labor and Delivery:** There are insufficient data to support the use of SUFENTA in labor and delivery. Therefore, such use is not recommended.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SUFENTA is administered to a nursing woman.

**Pediatric Use:** The safety and efficacy of SUFENTA in children under two years of age undergoing cardiovascular surgery has been documented in a limited number of cases.

**Animal Toxicology:** The intravenous $LD_{50}$ of SUFENTA is 16.8 to 18.0 mg/kg in mice, 11.8 to 13.0 mg/kg in guinea pigs and 10.1 to 19.5 mg/kg in dogs. Reproduction studies performed in rats and rabbits given doses of up to 2.5 times the upper human dose for a period of 10 to over 30 days revealed high maternal mortality rates due to decreased food consumption and anoxia, which preclude any meaningful interpretation of the results.

## ADVERSE REACTIONS

The most common adverse reactions of opioids are respiratory depression and skeletal muscle rigidity. See CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity.

The most frequent adverse reactions in clinical trials involving 320 patients administered SUFENTA were: hypotension (7%), hypertension (3%), chest wall rigidity (3%) and bradycardia (3%).

Other adverse reactions with a reported incidence of less than 1% were:
Cardiovascular: tachycardia, arrhythmia
Gastrointestinal: nausea, vomiting
Respiratory: apnea, postoperative respiratory depression, bronchospasm
Dermatological: itching
Central Nervous System: chills
Miscellaneous: intraoperative muscle movement

## DRUG ABUSE AND DEPENDENCE

SUFENTA (sufentanil citrate) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

## OVERDOSAGE

Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. However, no experiences of overdosage with SUFENTA have been established during clinical trials. The intravenous $LD_{50}$ of SUFENTA in male rats is 9.34 to 12.5 mg/kg (see ANIMAL TOXICOLOGY for $LD_{50}$s in other species). Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with SUFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdosage, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

## DOSAGE AND ADMINISTRATION

The dosage of SUFENTA should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs, and type of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

See dosage range chart for the use of SUFENTA by intravenous injection 1) in doses of up to 8 µg/kg as an analgesic adjunct to general anesthesia, and 2) in doses ≥8 µg/kg as a primary anesthetic agent for induction and maintenance of anesthesia with 100% oxygen.

**Usage in Children:** For induction and maintenance of anesthesia in children less than 12 years of age undergoing cardiovascular surgery, an anesthetic dose of 10-25 µg/kg administered with 100% oxygen is generally recommended. Supplemental dosages of up to 25-50 µg are recommended for maintenance, based on response to initial dose and as determined by changes in vital signs indicating surgical stress or lightening of anesthesia.

**Premedication:** The selection of preanesthetic medications should be based upon the needs of the individual patient.

**Neuromuscular Blocking Agents:** The neuromuscular blocking agent selected should be compatible with the patient's condition, taking into account the hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

**ADULT DOSAGE RANGE CHART**

| TOTAL DOSAGE | MAINTENANCE DOSAGE |
|---|---|
| **1-2 µg/kg:** administered with nitrous oxide/oxygen in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required. | **10-25 µg (0.2-0.5 ml):** as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia. Supplemental dosages should be individualized and adjusted to the remaining operative time anticipated. |
| **2-8 µg/kg:** administered with nitrous oxide/oxygen in patients undergoing more complicated major surgical procedures. At dosages in this range, SUFENTA has been shown to provide some attenuation of sympathetic reflex activity in response to surgical stimuli, provide hemodynamic stability, and provide relatively rapid recovery. | **25-50 µg (0.5-1 ml):** as determined by changes in vital signs that indicate stress or lightening of analgesia. Supplemental dosages should be individualized, and adjusted to the remaining operative time anticipated. |
| **8-30 µg/kg:** (anesthetic doses) administered with 100% oxygen and a muscle relaxant. SUFENTA has been found to produce sleep at dosages ≥8 µg/kg and to maintain a deep level of anesthesia without the use of additional anesthetic agents. At dosages in this range of up to 25 µg/kg, catecholamine release is attenuated. Dosages of 25-30 µg/kg have been shown to block sympathetic responses including catecholamine release. High doses are indicated in patients undergoing major surgical procedures, such as cardiovascular surgery and neurosurgery in the sitting position with maintenance of favorable myocardial and cerebral oxygen balance. Post-operative mechanical ventilation and observation are essential at these dosages due to extended postoperative respiratory depression. | **25-50 µg (0.5-1 ml):** as determined by changes in vital signs that indicate stress and lightening of anesthesia. |

In patients administered high (anesthetic) doses of SUFENTA, it is essential that qualified personnel and adequate facilities are available for the management of postoperative respiratory depression.

Also see WARNINGS and PRECAUTIONS sections.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

## HOW SUPPLIED

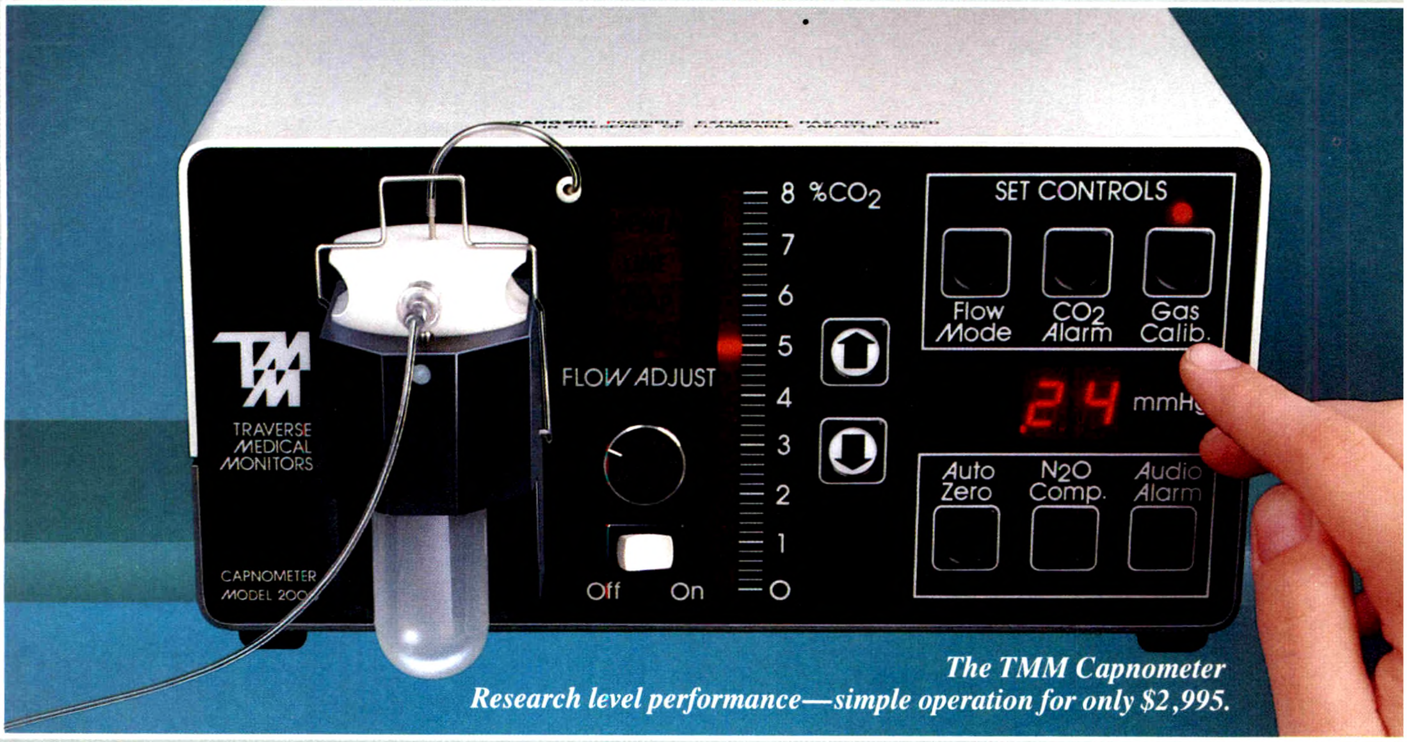
SUFENTA (sufentanil citrate) Injection for intravenous use is available as:

| | |
|---|---|
| NDC 50458-050-01 | 50 µg/ml, 1 ml ampoules in packages of 10 |
| NDC 50458-050-02 | 50 µg/ml, 2 ml ampoules in packages of 10 |
| NDC 50458-050-05 | 50 µg/ml, 5 ml ampoules in packages of 10 |

Protect from light. Store at room temperature.

JANSSEN
PHARMACEUTICA
Piscataway, N.J. 08854    U.S. Patent No. 3,998,834    7618501-M    May 1984, June 1984

# Forget your old ideas about capnometers.



***The TMM Capnometer***
***Research level performance—simple operation for only $2,995.***

# Ours is easy to use.

The TMM Capnometer is simple to operate. Just connect the Capnometer to the patient or the ventilator circuit, and turn it on. To set parameters, as illustrated by the gas calibration procedure above, you simply press tactile response buttons.

Thanks to a powerful microprocessor, the TMM Capnometer monitors itself so you can give more attention to your patient. The Capnometer alerts you when a trend has been determined that deviates from parameters you have established.

All user selected operating parameters are retained in memory. Automatic baseline updates provide long term unattended operation.

Data display is clear, bright, and continuous. A linearized signal output enables you to observe end-tidal waveforms.

An advanced Fluids Separator* on the TMM Capnometer continuously clears the gas stream of fluids.

A reliable infrared analyzer counts $CO_2$ molecules in under 100 msec at a flow rate of 260 ml/minute—a rate comparable to dedicated mass spectrometers and faster than multiplexed units.

The TMM Capnometer is backed by a comprehensive user support and service program. And it costs only $2,995.

Traverse
Medical
Monitors
TM™
A
SUBSIDIARY OF
DYNATECH CORPORATION

See us at the ASA Show—Booth 634.

*For more information, please contact:*
*Traverse Medical Monitors, 6812 South State Road, Saline, Michigan 48176*
*or call toll-free: (800) 247-7038 (800) 722-4153 in Michigan*

**patent pending*

# OTORHINOLARYNGOLOGY

## EXCERPTA MEDICA
## ABSTRACTS SECTION 11

**Excerpta Medica** abstracts articles from well over 3,500 biomedical, pharmaceutical and chemical journals, covering the most significant published papers in the field of biomedicine from all countries of the world.

- Abstracts are selected and indexed by practising medical specialists.
- Abstracts are arranged by major topics, giving the Abstracts Journals a concise, easy-to-read form.
- Each issue includes subject and author indexes.
- Detailed specialist indexing from multiple points of view makes it easy to find the right information in the shortest possible time.

***The Comprehensiveness of a Database – The Convenience of a Journal***

### OTORHINOLARYNGOLOGY SECTION 11

The information in this abstract journal is organized on an anatomical basis with separate chapters for each part of the body falling within the otorhinolaryngological area.
Particular attention is also given to the skull, face and mouth (including the teeth, tongue, salivary glands, etc.).

In addition there are special chapters for hearing, speech disorders, phoniatrics and otorhinolaryngological anesthesia.

### Editorial Board

**B.R. ALFORD** *Houston*
**S. VAN DER BAAN** *Amsterdam*
**J.C. BALLANTYNE** *London*
**E. BOCCA** *Milano*
**D.P. BRYCE** *Toronto*
**A. BUSTAMANTE BALCARCEL** *Mexico City*
**E. CERNÝ** *Prague*
**M. FEINMESSER** *Jerusalem*
**C.A. HAMBERGER** *Stockholm*
**D.F.N. HARRISON** *London*
**M. HINOKI** *Kyoto*
**H.P. HOUSE** *Los Angeles*
**E.H. HUIZING** *Utrecht*
**L.B.W. JONGKEES** *Amsterdam*
**H.K. KRISTENSEN** *Copenhagen*
**A.J.G. LEDOUX** *Liège*
**R.G. MACKAY** *Sydney*
**J. MARCO** *Sevilla*
**H. MASING** *Erlangen*
**M. MORIMOTO** *Kyoto*
**C.R. PFALTZ** *Basel*
**P. PIALOUX** *Paris*
**N.A. PREOBRAZENSKII** *Moscow*
**J.V. DE SA** *Bombay*
**B.H. SENTURIA** *St. Louis*
**U. SIIRALA** *Helsinki*
**A. SJÖBERG** *Stockholm*
**L. SURJAN** *Budapest*
**J.I. SUZUKI** *Tokyo*
**JUAN M. TATO** *Buenos Aires*
**N. TOROK** *Chicago*
**C.E. VISSER** *Amsterdam*
**F.Ø. WINTHER** *Oslo*
**A. ZAKREWSKI** *Poznan*

**Excerpta Medica Database**
Librarians and Information Officers may also be interested to know that the entire Excerpta Medica Database is also available on-line via many international database vendors, including DIALOG, BRS, DATASTAR and DIMDI. Full information is available by writing to:

The Marketing Director
Database Products,
P.O. Box 1527,
1000 BM AMSTERDAM,
The Netherlands.

**Subscription Information:**
**OTORHINOLARYNGOLOGY**
**SECTION 11**

*1985 Vol. 49*
*(1 vol. in 10 issues)*
*Price: US $235.25/Dfl. 633.00*
*including postage and handling.*
*ISSN 0014-4150*

For further information and/of free sample copy write to:

**EXCERPTA MEDICA**
ELSEVIER SCIENCE PUBLISHERS
P.O. Box 211, 1000 AE Amsterdam, The Netherlands or

In the U.S.A. & Canada
ELSEVIER SCIENCE PUBLISHERS
52 Vanderbilt Avenue, New York, NY 10017, U.S.A.

*The Dutch guilder price is definitive. US $ prices are subject to exchange rate fluctuations.*
*Prices are excl. B.T.W. for Dutch customers.*

FL 37A206

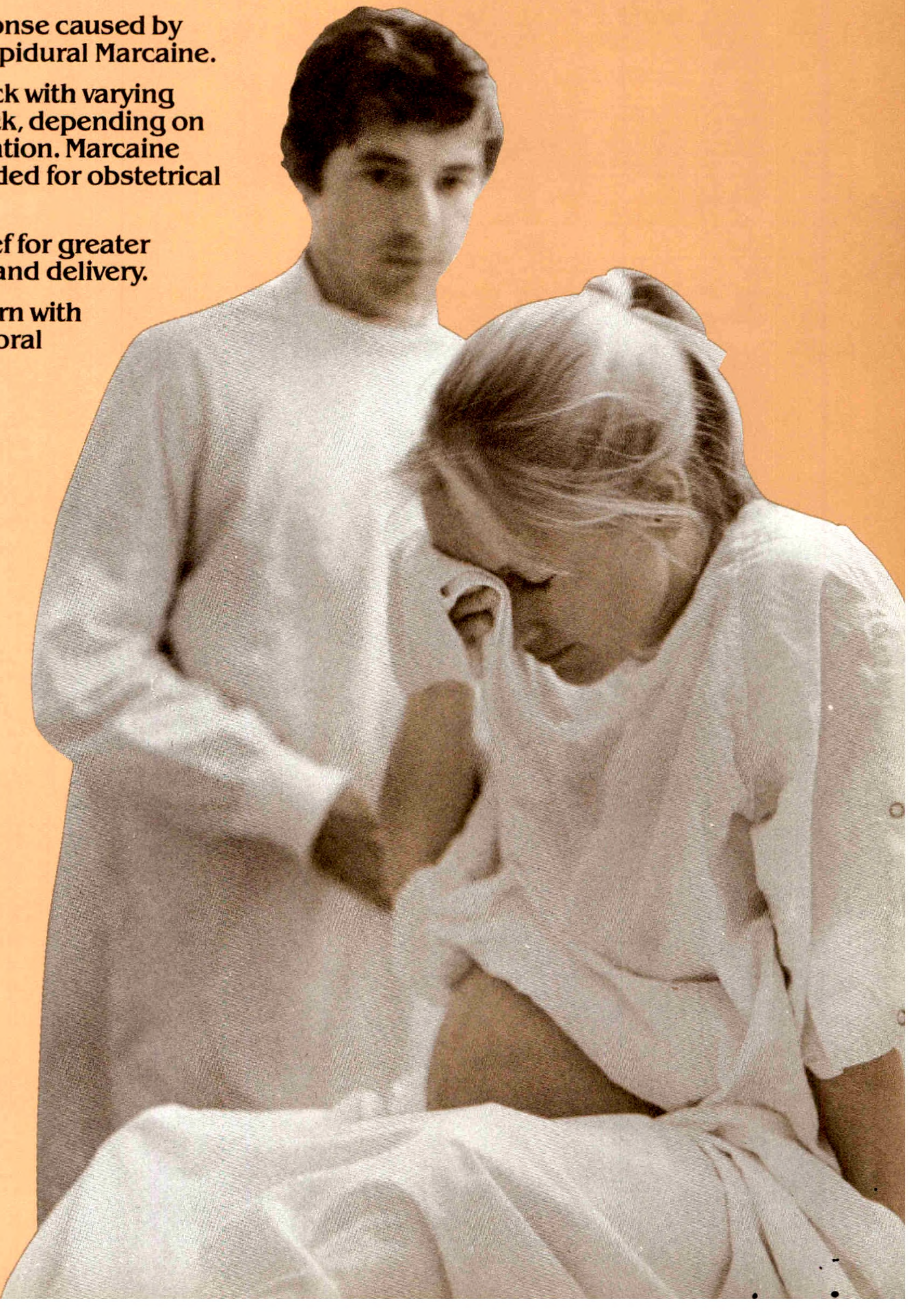
# Reduce Maternal and Fetal Stress.

## Marcaine® HCl 0.25% or 0.5%

(bupivacaine HCl injection, USP)

with or without epinephrine 1:200,000

- Break the stress response caused by unblocked pain with epidural Marcaine.
- Excellent sensory block with varying degrees of motor block, depending on dosage and concentration. Marcaine 0.75% not recommended for obstetrical anesthesia.
- Long lasting pain relief for greater comfort during labor and delivery.
- Proven safe for newborn with minimal neurobehavioral effects and minimal drug exposure.[1,2]



**Winthrop-Breon**

**WINTHROP-BREON LABORATORIES**
90 Park Avenue, New York, NY 10016

See adjacent page for important product information concerning contraindications, warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations.

Resuscitative equipment and drugs should be readily available when any local anesthetic is used.

Contraindicated for obstetric paracervical block.

©1984 Winthrop-Breon Laboratories

# Marcaine® HCl
## (bupivacaine HCl injection, USP) with or without epinephrine 1:200,000

**PLEASE CONSULT FULL PRESCRIBING INFORMATION. A SUMMARY FOLLOWS:**

**CONTRAINDICATIONS:** Obstetric paracervical block anesthesia; use in this technique has resulted in fetal bradycardia and death. Known hypersensitivity to the drug or to any amide-type local anesthetic, or to other components of MARCAINE solutions.

### WARNINGS

**THE 0.75% CONCENTRATION OF MARCAINE IS NOT RECOMMENDED FOR OBSTETRICAL ANESTHESIA. THERE HAVE BEEN REPORTS OF CARDIAC ARREST WITH DIFFICULT RESUSCITATION OR DEATH DURING USE OF MARCAINE FOR EPIDURAL ANESTHESIA IN OBSTETRICAL PATIENTS. IN MOST CASES, THIS HAS FOLLOWED USE OF THE 0.75% CONCENTRATION. RESUSCITATION HAS BEEN DIFFICULT OR IMPOSSIBLE DESPITE APPARENTLY ADEQUATE PREPARATION AND APPROPRIATE MANAGEMENT. CARDIAC ARREST HAS OCCURRED AFTER CONVULSIONS RESULTING FROM SYSTEMIC TOXICITY, PRESUMABLY FOLLOWING UNINTENTIONAL INTRAVASCULAR INJECTION. THE 0.75% CONCENTRATION SHOULD BE RESERVED FOR SURGICAL PROCEDURES WHERE A HIGH DEGREE OF MUSCLE RELAXATION AND PROLONGED EFFECT ARE NECESSARY.**

**LOCAL ANESTHETICS SHOULD ONLY BE EMPLOYED BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES WHICH MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED, AND THEN ONLY AFTER INSURING THE *IMMEDIATE* AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY RESUSCITATIVE EQUIPMENT, AND THE PERSONNEL RESOURCES NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES. (See also ADVERSE REACTIONS, PRECAUTIONS and OVERDOSAGE.) DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.**

Local-anesthetic solutions containing antimicrobial preservatives, ie, those supplied in multiple-dose vials, should not be used for epidural or caudal anesthesia because their safety has not been established with regard to intrathecal injection—intentionally or not.

It is essential that aspiration for blood or cerebrospinal fluid, where applicable, be done prior to injecting any local anesthetic (the original and all subsequent doses) to avoid intravascular or subarachnoid injection, which can occur even with a negative aspiration.

MARCAINE with epinephrine 1:200,000 or other vasopressors should not be used concomitantly with ergot-type oxytocic drugs, and used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types; severe prolonged hypertension may result.

Pending further experience, MARCAINE administration in children younger than 12 years is not recommended.

Mixing, or a prior or intercurrent use, of any other local anesthetic with MARCAINE cannot be recommended because such use lacks sufficient clinical data.

There have been reports of cardiac arrest and death with MARCAINE for intravenous regional anesthesia (Bier block). Since information on safe dosages and procedural techniques is lacking, MARCAINE is not recommended.

**PRECAUTIONS: General:** Safety and effectiveness of local anesthetics depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Resuscitative equipment, drugs, and oxygen should be available for immediate use. (See WARNINGS, ADVERSE REACTIONS, OVERDOSAGE.) During major regional nerve blocks, the patient should have I.V. fluids via an indwelling catheter to assure a functioning intravenous pathway. The lowest effective anesthetic dosage should be used to avoid high plasma levels and serious adverse effects.

**Epidural Anesthesia:** The 0.5% and 0.75% solutions should be administered in increments of 3-5 mL with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. Administration should be slow, with frequent aspirations before and during the procedure to avoid intravascular injection which is still possible even if aspirations for blood are negative. Syringe aspirations should also be performed before and during each supplemental injection by "continuous" (intermittent) catheter technique. During an epidural procedure, it is recommended that a test dose be administered initially and the effects monitored before giving the full dose. When using continuous catheter technique, test doses should be given prior to both the original and all reinforcing doses because plastic tubing in the epidural space can migrate into a blood vessel or through the dura. Clinical conditions permitting, the test dose should contain epinephrine (10-15 μg has been suggested) to provide warning of unintended intravascular injection. If injected into a blood vessel, this amount is likely to produce a transient "epinephrine response" within 45 seconds, consisting of an increase in heart rate and/or systolic blood pressure, circumoral pallor, palpitations, and nervousness in the unsedated patient who may exhibit only a pulse-rate increase of 20 or more beats per minute for 15 or more seconds. Therefore, following the test dose, heart rate should be monitored for any increase. Patients on beta blockers may not manifest such changes, but blood-pressure monitoring can detect a transient systolic rise. The test dose should also contain 10-15 mg of MARCAINE or an equivalent amount of another local anesthetic to detect unintended intrathecal injection. This will be evidenced within a few minutes by signs of spinal block (eg, decreased gluteal sensation, paresis of the legs or, in the sedated patient, absent knee jerk). Two or 3 mL of MARCAINE 0.5% with epinephrine 1:200,000 contain, respectively, 10 and 15 mg of bupivacaine HCl and 10 and 15 μg of epinephrine. An intravascular or subarachnoid injection is still possible even with negative results of the test dose, which itself may produce an epinephrine-induced cardiovascular or systemic toxic reaction or high spinal effect.

Repeated doses may cause significant increases in plasma levels with each such injection due to slow accumulation of the drug or its metabolites, or to slow metabolic degradation. Tolerance to elevated blood levels varies with the patient's status. Debilitated, elderly, and acutely ill patients should be given reduced doses commensurate with age and physical status. Also use local anesthetics with caution in patients with hypotension or heart block.

There should be careful and constant monitoring of the patient's cardiovascular and respiratory (adequacy of ventilation) vital signs and state of consciousness after each injection, and kept in mind at such times that restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be warnings of CNS toxicity.

Local anesthetic solutions with a vasoconstrictor should be used cautiously and carefully in body areas supplied by end arteries or with otherwise restricted blood supply (digits, nose, external ear, penis, etc.). Patients with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response; ischemic injury or necrosis may result.

Amide-type anesthetics such as MARCAINE are metabolized by the liver; these drugs (especially repeat doses) should be used cautiously in patients with hepatic disease. Because of an inability to metabolize local anesthetics normally, patients with severe hepatic disease are at greater risk of developing toxic plasma concentrations. Also use with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the drug's prolongation of A-V conduction.

Serious dose-related cardiac arrhythmias may occur if preparations containing epinephrine are employed in patients during or following administration of potent inhalation anesthetics. In deciding whether to use these agents concurrently, their combined action on the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection should be taken into account (when applicable).

Many drugs used in anesthesia conduction are potentially triggering agents for familial malignant hyperthermia. Because it is unknown whether amide-type anesthetics may trigger this reaction and because the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard management protocol be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure, and metabolic acidosis may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspect triggering agent(s), and prompt treatment including oxygen, dantrolene I.V. (see prescribing information before use), and other supportive measures.

**Use in Head and Neck Area:** Small doses of local anesthetics injected into the head and neck area, including retrobulbar, dental, and stellate ganglion blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. The injection procedures require the utmost care. Confusion, convulsions, respiratory depression, and/or respiratory arrest, and cardiovascular stimulation or depression have been reported. These reactions may be due to intra-arterial injection of the local anesthetic with retrograde flow to the cerebral circulation. They may also be due to puncture of the dural sheath of the optic nerve during retrobulbar block with diffusion of any local anesthetic along the subdural space to the midbrain. Patients receiving these blocks should have their circulation and respiration monitored and be constantly observed. Resuscitative equipment and personnel for treating adverse reactions should be immediately available. Dosage recommendations should not be exceeded. (See DOSAGE AND ADMINISTRATION.)

**Use in Ophthalmic Surgery:** With MARCAINE 0.75% for retrobulbar block, complete corneal anesthesia usually precedes onset of clinically acceptable external ocular muscle akinesia. Presence of akinesia alone determines readiness for surgery.

**Use in Dentistry:** Because of the long duration of anesthesia when MARCAINE 0.5% with epinephrine is used dentally, caution patients about inadvertent trauma to tongue, lips, and buccal mucosa; advise them not to chew solid foods or test the anesthetized area by biting or probing until anesthesia has worn off (up to 7 hours).

**Information for Patients:** When appropriate, inform them in advance of possible temporary loss of sensation and motor activity (usually in the lower body) following administration of caudal or epidural anesthesia, or other possible adverse occurrence noted in package insert.

**Clinically Significant Drug Interactions:** Administering local anesthetic solutions containing epinephrine or norepinephrine to patients receiving MAO inhibitors or tricyclic antidepressants may produce severe, prolonged hypertension. Thus concurrent use should generally be avoided; in situations when such therapy is necessary, careful monitoring is essential. Concurrent use of vasopressor and ergot-type oxytocic drugs may cause severe, persistent hypertension or cerebrovascular accident. Phenothiazines and butyrophenones may reduce or reverse epinephrine's pressor effect.

**Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Long-term studies in animals of most local anesthetics including bupivacaine have not been conducted. There is no evidence from human data that MARCAINE may be carcinogenic or mutagenic or that it impairs fertility.

**Pregnancy Category C:** Decreased pup survival in rats and an embryocidal effect in rabbits have been observed when bupivacaine was administered to either in doses comparable to 5 to 9 times the maximum recommended daily human dose (400 mg). There are no adequate and well-controlled studies in pregnant women of the drug's effect on fetal development, and potential fetal risk must be justified by potential benefit. This does not exclude use of MARCAINE at term for obstetric anesthesia or analgesia. (See Labor and Delivery.)

**Labor and Delivery:** SEE BOXED WARNING REGARDING OBSTETRIC USE OF 0.75% MARCAINE, and its contraindication in obstetric paracervical block. Local anesthetics cross the placenta rapidly and, when used for epidural, caudal, or pudendal block, can cause varying degrees of maternal, fetal, and neonatal toxicity. (See Pharmacokinetics in CLINICAL PHARMACOLOGY.) The incidence and degree of toxicity depend upon the procedure performed, and drug type, amount, and technique of administration. Adverse reactions in the parturient, fetus, and neonate involve alterations of the CNS, peripheral vascular tone, and cardiac function.

Maternal hypotension has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and left-side positioning will help prevent decrease in blood pressure. Fetal heart rate should be monitored continuously, preferably electronically. Epidural, caudal, or pudendal anesthesia may alter parturition through changes in uterine contractility or maternal expulsive efforts. Epidural anesthesia has been reported to prolong second-stage labor by removing the parturient's reflex urge to bear down, or by interference with motor function. Use of obstetric anesthesia may increase need for forceps assistance.

Some local anesthetic drugs may diminish muscle strength and tone for the first day or two of life. It is unreported with bupivacaine.

Of extreme importance: Avoid aortocaval compression of the gravid uterus during administration of regional block. To do this, maintain the parturient in the left lateral decubitus position, or place a blanket roll or sandbag beneath the right hip to displace the gravid uterus away from the great vessels.

**Nursing Mothers:** It is not known whether local anesthetics are excreted in human milk; because many drugs are, administer with caution.

**Pediatric Use:** Without further experience in children under 12, MARCAINE is not recommended for this group.

**ADVERSE REACTIONS:** A major cause of adverse reactions to amide-type local anesthetics is excessive plasma levels, possibly due to overdosage, unintentional intravascular injection, or slow metabolic degradation.

**Systemic:** The most common acute experiences, demanding immediate countermeasures, involve the CNS and cardiovascular systems. Adverse events are generally dose-related and due to high plasma levels which may result from overdosage, rapid absorption from the injection site, diminished tolerance, or unintentional intravascular injection of the solution. In addition to systemic dose-related toxicity, unintentional subarachnoid injection during performance of caudal or lumbar epidural block or nerve blocks near the vertebral column (especially in the head and neck region) may result in underventilation or apnea. Also, hypotension due to loss of sympathetic tone, and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia, may occur, leading to secondary cardiac arrest if untreated. Factors influencing plasma protein binding such as acidosis, systemic diseases which alter protein production or competition of other drugs for protein binding sites, may diminish individual tolerance.

**Central Nervous System:** Excitation and/or depression, restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly convulsions. Excitement may be transient, depression being the first manifestation of an adverse reaction. Drowsiness merging into unconsciousness and respiratory arrest may quickly follow. Other CNS effects may be nausea, vomiting, chills, pupillary constriction. Incidence of convulsions varies with the procedure used and total dose administered. In studies of epidural anesthesia, overt toxicity progressing to convulsions occurred in approximately 0.1% of procedures.

**Cardiovascular:** High doses of unintentional intravascular injection may lead to high plasma levels and related myocardial depression, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmia including ventricular tachycardia and ventricular fibrillation, and cardiac arrest. (See WARNINGS, PRECAUTIONS, OVERDOSAGE.)

**Allergic:** Rare, and may occur as a result of sensitivity to the local anesthetic or to other formulation ingredients such as the antimicrobial preservative methylparaben contained in multiple-dose vials or sulfites in epinephrine-containing solutions. Possible reactions: urticaria, pruritus, erythema, angioneurotic edema (including laryngeal), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, perhaps anaphylactoid symptoms (including severe hypotension). Cross-sensitivity among members of the amide-type anesthetic group reported; value of sensitivity screening is unestablished.

**Neurologic:** Incidence of adverse reactions associated with use of such drugs may be related to the total dose administered, and dependent upon the particular drug used, route of administration, and the patient's physical status. Many effects may be related to technique, with or without the drug being contributory.

In performing caudal or lumbar epidural block, occasional unintentional penetration of the subarachnoid space by catheter or needle may occur. Subsequent adverse effects may depend partially on the amount of drug administered intrathecally and physiologic and physical effects of dural puncture. High spinals are characterized by leg paralysis, loss of consciousness, respiratory paralysis, and bradycardia. Effects following epidural or caudal anesthesia may include: spinal block of varying magnitude (including high or total spinal block); hypotension secondary to spinal block, urinary retention; fecal and urinary incontinence; loss of perineal sensation and sexual function; persistent anesthesia, paresthesia, weakness, paralysis of the lower extremities, and loss of sphincter control—all of which may show slow, incomplete, or no recovery; headache; backache; septic meningitis; meningismus; slowing of labor; increased incidence of forceps delivery; cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid.

**OVERDOSAGE:** Acute emergency during therapeutic local anesthesia is generally related to high plasma levels or unintended subarachnoid injection of the solution. (See ADVERSE REACTIONS, WARNINGS, PRECAUTIONS.)

The first consideration in management is prevention, best accomplished by careful, constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each injection. At the first sign of change, administer oxygen. *The first step in the management of systemic toxic reactions, as well as underventilation or apnea due to unintentional subarachnoid injection of drug solution, consists of* ***immediate*** *attention to the establishment and maintenance of a patent airway and effective assisted or controlled ventilation with 100% oxygen with a delivery system capable of permitting immediate positive airway pressure by mask.* Endotracheal intubation may be indicated to meet the need for prolonged ventilatory support or if difficulty is encountered in the maintenance of a patent airway.

If necessary, use drugs to control convulsions. A 50-100 mg bolus I.V. injection of succinylcholine will paralyze the patient (without CNS or cardiovascular depression) and facilitate ventilation. A 5-10 mg I.V. bolus of diazepam, or 50-100 mg of thiopental, will permit ventilation and counteract CNS stimulation, but these drugs also depress CNS, respiratory and cardiac function, add to postictal depression, and may cause apnea. Intravenous barbiturates, anticonvulsant agents, or muscle relaxants should be administered only by those familiar with use. Immediately after institution of ventilatory measures, circulatory adequacy should be evaluated; supportive treatment may require administration of I.V. fluids and, when appropriate, a vasopressor dictated by the clinical situation (eg, ephedrine or epinephrine to enhance myocardial contractile force).

Recent clinical data from patients experiencing convulsions induced by local anesthetics demonstrated rapid development of hypoxia, hypercarbia, and acidosis; with bupivacaine, within a minute of onset. These observations suggest that $O_2$ consumption and $CO_2$ production are greatly increased during the convulsions and emphasize the importance of immediate ventilation with oxygen; if not treated effectively, convulsions and their complications plus myocardial depression from direct effects of the local anesthetic may result in cardiac arrhythmias, bradycardia, asystole, ventricular fibrillation, or cardiac arrest. Respiratory abnormalities including apnea may occur; underventilation or apnea due to unintentional subarachnoid injection of the solution may also lead to these signs and cardiac arrest if ventilatory support is not instituted. If cardiac arrest occurs, prolonged resuscitative effort may determine a successful outcome.

In treating systemic toxicity, maternal hypotension, or fetal bradycardia following regional block, avoid aortocaval compression by the gravid uterus. The supine position is dangerous in pregnant women. The parturient should be maintained in the left lateral decubitus position if possible, or manual displacement of the uterus off the great vessels be accomplished. (See Labor and Delivery in PRECAUTIONS.)

**Composition of Marcaine Solutions:** 0.25%—each mL contains 2.5 mg bupivacaine; 0.5%—each mL contains 5 mg bupivacaine; 0.75%—each mL contains 7.5 mg bupivacaine. All concentrations contain NaCl for isotonicity in Water for Injection.

In multiple-dose vials, each mL also contains 1 mg methylparaben. With epinephrine, each mL also contains 0.0091 mg epinephrine bitartrate, 0.5 mg sodium bisulfite, 0.001 mL monothioglycerol, 2 mg ascorbic acid, 0.0017 mL 60% sodium lactate, and 0.1 mg edetate calcium disodium.

1. Ostheimer GW: Neurobehavioral effects of local anesthesia and fetal resuscitation. *Reg Anesth* 1981;6:136-145.
2. Naulty JS, Ostheimer G, Datta S, et al: Bupivacaine in breast milk following epidural anesthesia for vaginal delivery. Presented as a scientific poster at the Annual Meeting of the American Society of Regional Anesthesia, Lake Buena Vista, FL, March 23-27, 1983.

Winthrop-Breon

WINTHROP-BREON LABORATORIES
Division of Sterling Drug Inc
90 Park Avenue
New York, NY 10016

ANESTH ANALG 849
1985;64:849–50

# Editorial

# Fresh Frozen Plasma:

## Too Few Indications—Too Much Use

Do clinicians overuse fresh frozen plasma (FFP)? A continuing series of reports (1–4), mostly authored by blood bankers, suggests that they do, and now a Consensus Development Conference sponsored by the National Institutes of Health agrees (5). A panel of experts, including surgeons, anesthesiologists, hematologists and community representatives has concluded that

> the administration of FFP has increased dramatically in recent years despite the paucity of definitive indications for its use,
>
> there is no justification for the use of FFP as a volume expander or as a nutritional source,
>
> there is no documentation that FFP has a beneficial effect when used as part of the transfusion management of patients with massive hemorrhage,
>
> there is no evidence that the prophylactic administration of FFP decreases transfusion requirements in multiple transfused patients who do not have documented coagulation defect, and
>
> there is little scientific evidence to support the increasing use of FFP in clinical medicine.

Not only did the Consensus Development Conference stress the relative paucity of indications for FFP, but it also reminded clinicians of the risks associated with its use. These include transmission of diseases such as hepatitis and possibly AIDS, as well as severe and occasionally fatal anaphylactoid reactions. Because of the continuing widespread use of FFP despite its potential for serious complications and the relatively poor documentation of benefit, the conference also suggested that educational efforts be directed to students and to clinicians who use FFP.

Most FFP is given to surgical patients, and a large proportion is used either during or shortly after the surgical procedure. For that reason anesthesiologists are one group who need to know clearly when FFP is indicated and when it is not.

Perhaps the most widespread misuse of FFP occurs when it is used arbitrarily in an attempt to prevent the development of factor deficiencies during blood replacement. Such an approach has no benefit (6) and has been singled out by the panel as unjustified unless factor deficiencies are present and presumed to be the "sole or principle derangement." Anesthesiologists in particular should not consider FFP as a routine part of any replacement program, but should reserve its use for those cases in which there is both diffuse abnormal bleeding and documented coagulopathy. There is no justification for applying a potentially lethal therapy in the absence of clear-cut and unequivocal indications. These do not exist for the prophylactic use of FFP, and its use in such settings is contraindicated and improper.

The conference addressed the concern that much FFP is cotransfused with red blood cells to provide a whole blood substitute and reminded clinicians that safer alternatives for volume replacement exist. Although red blood cell transfusions are needed to restore deficient oxygen carrying capacity, circulating volume defects should be restored with colloids other than FFP or with crystalloid. There is no rationale for attempting to reconstitute whole blood by the simultaneous infusion of red cells and FFP.

What, then, is the appropriate role for FFP in current practice? It can and should be used to replace isolated factor deficiencies, for example, Factor V or Factor XI, when specific concentrates are not available. It can be used when there is widespread bleeding and a documented coagulopathy, although many such patients will be thrombocytopenic and better served by platelet transfusions (7). Its use in actively bleeding patients with liver disease and a secondary coagulopathy may be justified, although adequate documentation of its value is not available. In such patients, however, relatively large volumes and rapid infusion are required.

There is little in the medical literature or in the great

© 1985 by the International Anesthesia Research Society

storehouse of "clinical experience" to suggest that FFP has a major role in bleeding surgical patients. Why its use has grown is an enigma, but it suggests that clinicians who face difficult situations respond by trying to "do something." The time has come to perform additional controlled clinical experiments similar to those that have been recently reported (6) and to heed the data generated by them. We are past the time when any therapy—especially one as costly and as potentially dangerous as FFP—should be undertaken without better evidence of its efficacy.

Joseph R. Bove, MD
*Department of Laboratory Medicine*
*Yale University School of Medicine*
*New Haven, CT*

## References

1. Kahn RA, Staggs SD, Meller WV, Ellis FR. Use of plasma products with whole blood and packed rbcs. JAMA 1979;242:2087–90.
2. Gilbert JA, Bove JR, Dubin S, Bush WS. Patterns of frozen plasma use. Conn Med 1981;45:507–11.
3. Gross SJ, Filston HC, Anderson JC. Controlled study of treatment for disseminated intravascular coagulation. J Pediat 1982;100:445–8.
4. Braunstein AH, Oberman HA. Transfusion of plasma components. Transfusion 1984;24:281–6.
5. Fresh-frozen plasma. Indications and risks. Consensus Conference, NIH. JAMA 1985;253:551–3.
6. Mannucci PM, Federici AB, Serchia G. Hemostasis testing during massive blood replacement. A study of 172 cases. Vox Sang 1982;42:113–23.
7. Counts RB, Haisch C, Simon TL, Maxwell NC, Hermbach DM, Carrico CJ. Hemostasis in massively transfused trauma patients. Ann Surg 1973;190:91–9.

ANESTH ANALG 1985;64:851-6

# Morphine–Caffeine Analgesic Interaction in Rats

Donald L. Person, MD, Igor Kissin, MD, PhD, Pamela T. Brown, BS, Anne V. Xavier, MD, H. Ronald Vinik, MD, and Edwin L. Bradley, PhD

PERSON DL, KISSIN I, BROWN PT, XAVIER AV, VINIK HR, BRADLEY EL. Morphine–caffeine analgesic interaction in rats. Anesth Analg 1985;64:851–6.

*The ability of caffeine to modify the effect of morphine on motor response to noxious stimulation was studied in 195 rat experiments. Motor reaction responses to noxious stimuli were studied in three series of experiments with three different techniques of mechanical tail stimulation. In each series of experiments, dose–response curves for morphine (probit analysis) were determined with and without the addition of caffeine (30 mg · kg*$^{-1}$*). It was found that caffeine decreased morphine ED*$_{50}$* values in all three series of experiments, from 1.1 to 0.6 mg · kg*$^{-1}$* (*$P < 0.002$*), from 3.2 to 2.5 mg · kg*$^{-1}$* (*$P < 0.01$*), and from 13.2 to 6.2 mg · kg*$^{-1}$* (*$P < 0.002$*). When caffeine was used alone in a dose of 30 mg · kg*$^{-1}$*, there were no significant changes in motor reaction responses with any of the three methods applied for the assessment of morphine–caffeine combinations. These data indicate that caffeine potentiates the inhibitory effect of morphine on motor response to noxious stimulation in rats. It has been suggested that the effect of morphine on the motor response to somatic noxious stimulation results primarily from activation of inhibitory control systems concerned with this response. Caffeine may modulate the antinociceptive effect of morphine by stimulating one of these systems.*

Key Words: ANALEPTICS—caffeine. ANALGESICS—morphine. INTERACTIONS (DRUG)—caffeine–morphine.

Recently it was found that caffeine strengthens the effect of morphine on the cardiac acceleration response to noxious stimulation in rat experiments (1). Early studies reported that another CNS stimulant—dextroamphetamine—enhances the analgesic effect of morphine in dogs and mice (2,3). It was also shown that the simultaneous administration of dextroamphetamine in human volunteers enhances the effect of morphine on experimental pain (4), and the combination of dextroamphetamine and morphine was suggested for treatment of postoperative pain (5). Impressive new evidence exists for the efficacy of caffeine as an analgesic adjuvant to acetaminophen, aspirin, or their combination in patients with postpartum uterine cramping or episiotomy pain (6).

The question arises as to whether the ability of caffeine to potentiate the antinociceptive effect of morphine is restricted to only the area of cardiovascular responses (1), or whether it may also manifest itself when somatic responses to painful stimulation are concerned. In the latter case, caffeine may be regarded as an analgesic adjuvant not only to analgesic-antipyretics; the possibility of its use as an analgesic adjuvant to opioids also should be considered. The aim of the present study was to demonstrate that caffeine can strengthen the effect of morphine on somatic responses to noxious stimulation.

## Methods

Experiments were performed on 195 male Sprague–Dawley rats weighing 275–350 g. The effects of morphine–caffeine combinations on somatic response to noxious stimulation were studied using two methods: gradual compression test suggested by Green et al. (motor reaction threshold to pressure (7)), and a modified Haffner technique (motor response to tail-clamp (8)).

Reaction threshold was determined with an Analgesy-meter (Ugo Basile, Milan, Italy), a device that provides increasing pressure. The rat's tail was positioned on a Teflon platform and the pressure plate (0.7 mm edge) attached to the device was placed 1–2 cm from the tip of the tail (the rat was held by the experimenter's hand). Pressure was increased at a constant rate of 80 g/sec until the animal made an attempt to escape (coordinated struggle). The pressure at that moment was recorded, and the mean of

---

Received from Pain Research Center, Department of Anesthesiology, University of Alabama at Birmingham, Birmingham, Alabama. Accepted for Publication April 12, 1985.

Address correspondence to Dr. Kissin, Department of Anesthesiology, University of Alabama at Birmingham, University Station, Birmingham, AL 35294.

© 1985 by the International Anesthesia Research Society

Table 1. Series of Experiments

| Series | Number | Methods | Agents |
|---|---|---|---|
| I | 20 | Motor reaction threshold to gradual tail-compression[a] (graded response) | Caffeine |
| I(*A*) | 10 | Vocalization threshold to electrical tail-stimulation (graded response) | Caffeine |
| I(*B*) | 10 | Tail-flick to hot water (graded response) | Caffeine |
| II | 50 | Motor reaction to gradual tail-compression[a] with cutoff pressure of 619 g (quantal response) | Morphine vs morphine–caffeine |
| III | 50 | Motor reaction to gradual tail-compression[a] with cutoff pressure of 1240 g (quantal response) | Morphine vs morphine–caffeine |
| IV | 55 | Motor reaction to tail-clamp (quantal response) | Morphine vs morphine–caffeine |

[a] Compression with the use of "Analgesy-meter." See explanations in Methods.

three consecutive measurements was taken as the individual reaction threshold. The reaction threshold was determined in control and treated animals (graded response to an agent).

In the series of experiments in which analgesic action was assessed as a quantal response to an agent (with probit analysis), the following two approaches were used to obtain quantal data. In a group of 20 nontreated rats, the mean reaction threshold to pressure was determined, which was equal to 431 g with the standard deviation 94 g. With the first approach (9), the effect in the treated animal was designated positive if the individual reaction threshold to pressure exceeded the nontreated group mean threshold by two standard deviations of the mean. This resulted in a cutoff pressure of 619 g (431 + 94 × 2 = 619 g). With the second approach, the cutoff pressure was doubled; and, therefore, if an animal did not respond to pressure less than 1240 g, the effect was scored as positive.

With the Haffner technique, noxious stimulation was induced by placement of a hemostat on the tail (pressure of 0.3 kg/mm$^2$) for 60 sec. In nontreated rats, this stimulation always caused immediate biting of the hemostat. Only the absence of purposeful movement response to stimulation was considered a positive effect of a dose. The use of the three tests—reaction threshold with cutoff pressures of 619 g and 1240 g as well as tail-clamp technique—resulted in application of different intensities of noxious stimulation that gave the opportunity to study caffeine–morphine interaction at different dosage levels of morphine.

During the course of the study, we found that there was a need for two additional series of experiments with caffeine alone. The following two methods were used in these series: tail-flick to hot water (10) and vocalization response to electrical tail stimulation (11). With the tail-flick method, the rat's tail was put into water maintained at 55°C, and the reaction time for its withdrawal after immersion was recorded. With electrical tail stimulation, the electrodes were placed in the tail at a distance of 2 cm apart. Stimulation was provided by a Grass S88 stimulator with the following parameters: frequency, 125 Hz; stimulus duration, 1.6 msec; duration of stimulation, 1 sec. Stimulus intensity was gradually increased in steps of 0.25 V until an animal responded with a squeak.

The series of experiments performed are listed in Table 1. In series I, the effect of caffeine on motor reaction threshold to gradual tail compression was studied in four groups of animals receiving 0 mg · kg$^{-1}$ (control); 10 mg · kg$^{-1}$; 30 mg · kg$^{-1}$; and 100 mg · kg$^{-1}$ of caffeine. Each group consisted of five animals; caffeine was injected intraperitoneally 30 min before testing. In the control group, animals received an injection of saline. Because results obtained in this series of experiments were in disagreement with the results reported by Paalzow and Paalzow (11), who used an electrical tail stimulation for reaction threshold measurements, two additional series of experiments were performed. In one of these, vocalization threshold to electrical tail stimulation (I(*A*)) was used. Caffeine was administered in a dose of 100 mg · kg$^{-1}$, intraperitoneally, 30 min before testing. Control (saline) and treated groups (five animals in each) were compared. The method, the dose of caffeine, and the time interval after injection were chosen to have conditions similar to those giving maximal effect in the Paalzow and Paalzow experiments. In experiments with tail-flick to hot water (I(*B*)), two groups of five animals were used—control (saline) and caffeine (100 mg · kg$^{-1}$, intraperitoneally, 30 min before testing).

In series II, the effect of caffeine on the morphine dose–response curve was investigated for the reaction threshold with a cutoff pressure of 619 g. There were two subseries of experiments, one with morphine alone and another with morphine–caffeine combinations. The dose–response curve for morphine was determined as described in our previous experiments (12).

Briefly, five groups of five rats constituted a morphine dose–response curve. In one group of animals, the dose of morphine was low enough so that all animals were unaffected, and in another group, it was high enough so that all were affected. Dose levels for these two groups were determined in preliminary experiments. In the three remaining groups, the doses of the drug were spaced between the above mentioned marginal doses. When morphine was used with caffeine, the dose of caffeine was kept constant in all five groups of rats. Both morphine and caffeine were injected intraperitoneally, 30 min before testing (when morphine was used alone, an injection of saline served as a substitute for the injection of caffeine). For the subseries of experiments in which morphine was used alone (five groups of animals), its doses were 0.6, 0.8, 1.0, 1.3, and 1.5 mg · $kg^{-1}$. In another subseries of experiments, with the addition of caffeine, morphine doses were 0.4, 0.5, 0.6, 0.8, and 1.0 mg · $kg^{-1}$. Caffeine was added in a dose of 30 mg · $kg^{-1}$ for all five groups of animals.

In series III, the effect of caffeine on the morphine dose–response curve was investigated with a doubled cutoff pressure (1240 g). This allowed the investigation of morphine–caffeine interaction at much higher doses of morphine. In the subseries of experiments where morphine was used alone, its doses were 2.0, 2.5, 3.0, 4.0, and 5.0 mg · $kg^{-1}$. In the subseries of experiments with the addition of caffeine (30 mg · $kg^{-1}$), morphine doses were 2.0, 2.2, 2.5, 3.0, and 4.0 mg · $kg^{-1}$.

In series IV, the effect of caffeine on the morphine dose–response curve was investigated by use of the Haffner technique. This technique allowed us to study the morphine–caffeine interaction at even higher doses than those in series III. In the subseries in which morphine was used alone, its doses were 7, 10, 15, 20, and 30 mg · $kg^{-1}$. In the subseries with caffeine (30 mg · $kg^{-1}$) added, morphine doses were 2, 3, 7, 10, 15, and 20 mg · $kg^{-1}$. Morphine sulfate was obtained from Mallincroft and caffeine from Sigma. Injection volumes ranged from 0.3–0.4 ml for morphine and 0.4–0.5 ml for caffeine or saline.

In the graded data analysis, the differences among the means of each dosage level were compared by one-way analysis of variance. Pairwise comparisons between means of caffeine and control groups were made by Fisher's protected least significant difference test. In the quantal data analysis, the probit method was used (13). The $ED_{50}$ values were compared via an asymptotic normal test for regression estimates. Calculations were performed on an IBM 4381 computer. Animal care standards in this study were in accordance with federal and institutional policy and standards of the American Association for Accreditation of Laboratory Animal Care as specified in the *Guide for Care and Use of Laboratory Animals* (14).

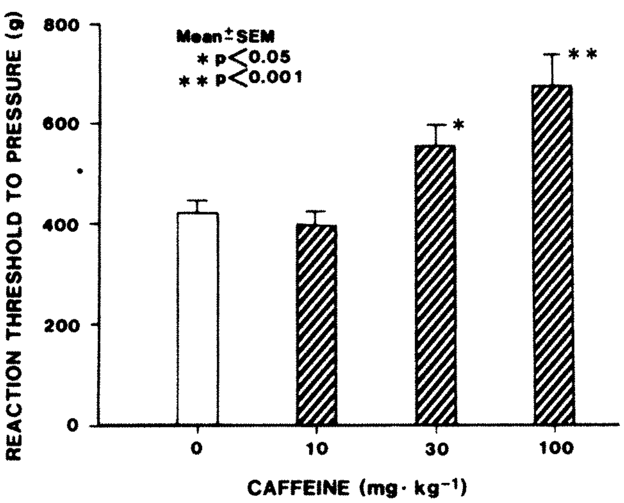


Figure 1. The effect of caffeine on reaction threshold to pressure. The open column represents the control (saline) group (5 animals), each hatched column represents a group of five animals receiving 10, 30, and 100 mg · $kg^{-1}$ of caffeine, respectively.

## Results

Figure 1 shows the effect of caffeine on motor reaction threshold to gradual tail compression. Caffeine in doses 30 and 100 mg · $kg^{-1}$ caused a significant increase in the threshold from 421 ± 21 g (control group) to 553 ± 44 g ($P < 0.05$) and 672 ± 64 ($P < 0.001$), respectively (M ± SEM).

In experiments with vocalization threshold to electrical tail stimulation, caffeine (100 mg · $kg^{-1}$), in contrast to the previous series of experiments, decreased the reaction threshold (by 61%, $P < 0.01$). At the same time, when tail-flick response to hot water was used, caffeine (100 mg · $kg^{-1}$) increased the reaction time (by 60%, $P < 0.05$), which was indicative of the analgesic action.

The results of the study of caffeine–morphine interaction are presented in Table 2. $ED_{50}$ values for morphine obtained in all three series of experiments (series II, III, and IV, see Table 1) were significantly decreased when caffeine (30 mg · $kg^{-1}$) was added. The changes were the following: from 1.1 to 0.6 mg · $kg^{-1}$ ($P < 0.002$); from 3.2 to 2.5 mg · $kg^{-1}$ ($P < 0.01$); and from 13.2 to 6.2 mg · $kg^{-1}$ ($P < 0.002$). The above $ED_{50}$ values were obtained from the dose–response curve data. Figure 2 illustrates the morphine dose–response curve with and without the addition of caffeine obtained in one of these three series of experiments (motor reaction to gradual tail

Table 2. The Effect of Caffeine on the Analgesic Activity of Morphine

| Test | Modulator | Number | Morphine $ED_{50}$ ($mg \cdot kg^{-1}$)[c] | $P$ value |
|---|---|---|---|---|
| Motor reaction to gradual tail compression with cutoff pressure 619 g[a] | None | 25 | 1.1 (0.8–1.4)[d] | $P < 0.002$ |
| | Caffeine[b] | 25 | 0.6 (0.5–0.8) | |
| Motor reaction to gradual tail compression with cutoff pressure of 1240 g[a] | None | 25 | 3.2 (2.6–3.9) | $P < 0.01$ |
| | Caffeine[b] | 25 | 2.5 (2.1–2.9) | |
| Motor reaction to tail clamp | None | 25 | 13.2 (9.5–17.3) | $P < 0.002$ |
| | Caffeine[b] | 30 | 6.2 (3.5–9.4) | |

[a] See explanation in the Methods. [b] Caffeine 30 $mg \cdot kg^{-1}$, intraperitoneally, 30 min before the test. [c] Morphine was injected intraperitoneally, 30 min before the test. [d] 95% fiducial limits.

compression with cutoff pressure of 619 g). As one can see, caffeine moved the morphine dose–response curve to the left along the dose axis. It strengthened the effect of morphine on motor response to gradual tail compression.

## Discussion

We have found that caffeine, in doses of 30 and 100 $mg \cdot kg^{-1}$, increased motor reaction threshold to gradual tail compression. This was a relatively mild increase in the threshold measured as a graded response to the agent. With the assessment of analgesic action in the quantal form, 30 $mg \cdot kg^{-1}$ of caffeine increased the threshold above the first cutoff pressure level (619 g) in only one of five rats, the 100 $mg \cdot kg^{-1}$ of caffeine increased the threshold above the first cutoff pressure level in three of five rats. Neither the gradual compression test, with quantal approach at the second cutoff pressure level (1240 g), nor the tail-clamp test showed any analgesic effect of caffeine.

Paalzow and Paalzow (11) reported that caffeine (25–100 $mg \cdot kg^{-1}$, intraperitoneally) decreased the thresholds for motor and vocalization responses to electrical tail stimulation in rats. Because the changes of the thresholds after caffeine administration obtained in the experiments of Paalzow and Paalzow and in our study were in opposite directions, we carried out two additional series of experiments. One series was performed with the method of electrical tail stimulation. This series of experiments resulted in findings very similar to those reported by Paalzow and Paalzow: caffeine (100 $mg \cdot kg^{-1}$) produced a decrease (by 61%) in the vocalization threshold to electrical tail stimulation. When another method of assessing analgesic activity was used, tail-flick response to hot water, 100 $mg \cdot kg^{-1}$ of caffeine caused an effect compatible with that obtained in compression test experiments: an increase in tail-withdrawal reaction time. The ability of agents with analgesic activity to produce different results with different pain tests is well known (15–17). Melzack et al. are of the opinion that the differences in the type of noxious stimulation and in motor responses required in various pain tests are crucial in determining analgesic influence (16). It is also possible to suggest that, with electrical tail stimulation, the well-known stimulatory effect of caffeine on the locomotor activity can somehow disguise its analgesic effect. Morichi and Pepeu (18), who used electrical tail stimulation to study hydroxyzine–morphine interaction, have found that this test, in contrast to the tail flick method, was not very specific for detecting antinociceptive action. They suggested that electrical tail stimulation "appears to be affected by drugs acting outside the nociceptive system."

Three approaches used in this study for the determination of morphine dose–response curves (gradual compression test with two cutoff pressures and tail clamp test) resulted in morphine $ED_{50}$ values of 1.1., 3.2, and 13.2 $mg \cdot kg^{-1}$. These values occurred within the range of reported analgesic doses for morphine in rodents with the intraperitoneal route of drug administration (19–23). The use of three morphine dose–response curves allowed us to investigate the ability of caffeine to interact with various doses of morphine from relatively small doses to large ones that are required to block very strong noxious stimulation.

With all three approaches, it was found that caffeine (30 $mg \cdot kg^{-1}$) strengthened the analgesic action of morphine. Morphine $ED_{50}$ values were decreased by 45, 22, and 53%. The caffeine dose of 30 $mg \cdot kg^{-1}$ was chosen for the study of morphine–caffeine interaction because it produced a mild effect on the reaction threshold (an increase in reaction threshold from 421 ± 21 to 553 ± 44 g, $P < 0.05$). In the approaches where analgesic action was assessed as a quantal response to an agent, this mild effect of caffeine was undetectable when given alone. Therefore, the increase in morphine analgesic activity with the addition of caffeine should be regarded as potentiation.

It previously was reported that caffeine strengthened the effect of morphine on cardiac acceleration

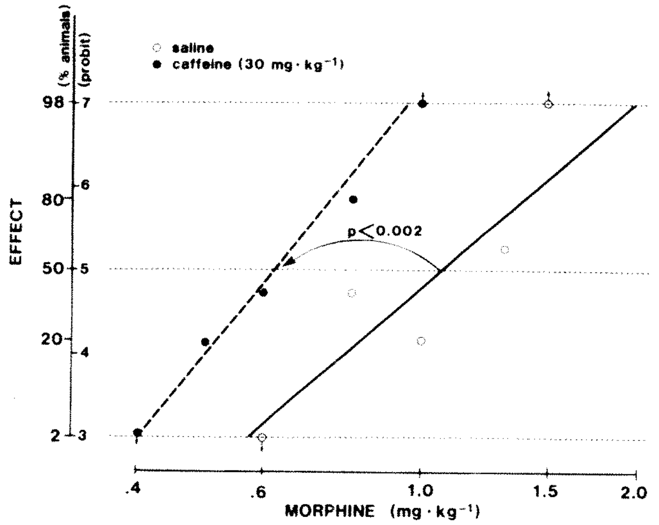


Figure 2. The effect of caffeine on the morphine dose-response curve for motor reaction to tail compression. Analgesic action was assessed as a quantal response to the agent. The effect in a treated animal was designated as positive if individual reaction threshold to pressure exceeded the nontreated group mean threshold by two standard deviations of the mean (cutoff pressure of 619 g, see Methods for explanations). The vertical axis shows the percentage of animals with reaction threshold that was above the cutoff pressure level (probit scale). Each dot represents a group of five animals at the indicated dosages (log scale).

response to noxious stimulation in rats (1). This study shows that the ability of caffeine to potentiate the antinociceptive effect of morphine is not restricted only to one specific area; it is related to both somatic and autonomic responses to noxious stimulation.

Impressive new evidence exists for the efficacy of caffeine as an analgesic adjuvant for acetominophen and aspirin in patients with acute pain (6). The ability of caffeine to potentiate the effect of aspirin also was reported in rat experiments including the use of inflamed paw pressure technique (24). The authors also reported that caffeine potentiates the antiinflammatory action of aspirin. They suggested that potentiation of the antiinflammatory activity probably accounts for the potentiated analgesia produced by the combination of aspirin and caffeine. The ability of caffeine to strengthen the analgesic effect of morphine, in our experiments, suggests that the central action of caffeine may be at least partially involved in a similar outcome of caffeine–aspirin analgesic interaction.

It has been reported that another CNS stimulant—dextroamphetamine—enhances the analgesic effect of morphine. This effect was confirmed in experiments using humans and animals (2–5,25). Amphetamine, in contrast to caffeine, has an adrenergic mechanism of action. However, it should be kept in mind that methylxanthines are able to increase the central noradrenaline turnover (26–28). In recent years, it has been shown that there are multiple adrenergic and nonadrenergic control systems modulating the antinoceptive effect of morphine (29–31). Caffeine may modulate the antinociceptive effect of morphine by stimulating one of these systems.

Rat experimental data and human clinical experience are difficult to correlate. From the present study it is possible to conclude only that caffeine, in terms of biological activity, has the potential to modulate the analgesic effect of morphine. It remains to be proven that this potential can manifest itself in clinical situations.

In conclusion, our data indicate that caffeine potentiates the inhibitory effect of morphine on motor response to noxious stimulation in rats.

## References

1. Kissin I, Jebeles JA. Pentobarbital antagonizes the effect of morphine on cardiac acceleration response to noxious stimulation. Anesth Analg 1984;63:669–72.
2. Goetzl FR, Burrill DY, Ivy AC. Analgesic effect of dextroamphetamine alone and in combination with morphine sulfate. Fed Proc 1943;2:16.
3. Goetzl FR, Burrill DY, Ivy AC. The analgesic effect of morphine alone and in combination with dextro-amphetamine. Proc Soc Exp Biol Med 1944;55:248–250.
4. Ivy AC, Goetzl FR, Burrill DY. Morphine-dextro-amphetamine analgesia. War Medicine 1944;6:67–71.
5. Forrest WH Jr, Brown BW, Brown CR, et al. Dextro-amphetamine with morphine for the treatment of postoperative pain. N Engl J Med 1977;296:712–5.
6. Laska EM, Abraham S, Mueller F, et al. Caffeine as an analgesic adjuvant. JAMA 1984;251:1711–8.
7. Green AF, Young PA. A comparison of heat and pressure analgesiometric methods in rats. Br J Pharmacol 1951;6:572–85.
8. Haffner F. Experimentelle Pruefung schmerzstillender Mittel. Dtsch Med Wochenschr 1929;55:731–3.
9. Swingle KF, Grant TJ, Kvan DC. Quantal responses in the Randall–Sellito assay (35615). Proc Soc Exp Biol Med 1971;137:536–8.
10. Janssen PAJ, Neimegeers CJE, Dony JGH. The inhibitory effect of fentanyl and other morphine-like analgesics on the warm water induced tail withdrawal reflex in rats. Arzneimittel-Forschung 1963;13:502.
11. Paalzow G, Paalzow L. The effects of caffeine and theophylline on nociceptive stimulation in the rat. Acta Pharmacol Toxicol 1973;32:22–32.
12. Kissin I, Kerr CR, Smith LR. Assessment of anaesthetic action of morphine and fentanyl in rats. Can Anaesth Soc J 1983;30:623–8.
13. Finney DJ. Probit analysis. London: Cambridge University Press, 1952.
14. Guide for the care and use of laboratory animals. DHEW Publication No (NIH) 78–23. Washington, DC:US Government Printing Office, 1978.
15. Dennis SG, Melzack R, Gutman S, Boucher F. Pain modulation by adrenergic agents and morphine as measured by three pain tests. Life Sci 1980;26:1247–59.

16. Dennis SG, Melzack R. Pain modulation by 5-hydroxytryptaminergic agents and morphine as measured by three pain tests. Exp Neurol 1980;69:260–70.
17. Cohen SR, Abbott FV, Melzack R. Unilateral analgesia produced by intraventricular morphine. Brain Res 1984;303:277–87.
18. Morichi R, Pepeu G. A study of the influence of hydroxyzine and diazepam on morphine antinociception in the rat. Pain 1979;7:173–80.
19. D'Amour FE, Smith DL. A method for determining loss of pain sensation. J Pharmacol Exp Ther 1941;72:74–9.
20. Bonnycastle D, Cook L, Ipsen J. The action of some analgesic drugs in intact and chronic spinal rats. Acta Pharmcol Tox (Kbh) 1953;9:332.
21. Bianchi C, Franceschini J. Experimental observations on Haffner's method for testing analgesic drugs. Br J Pharmacol 1954;9:280–4.
22. Proudfit HK, Anderson EG. Morphine analgesia: blockade by raphe magnus lesions. Brain Res 1985;98:612–8.
23. Leander JD. Comparison of morphine, meperidine, anileridine, and alphaprodine on schedule-controlled responding and analgesia. Pharmacol Biochem Behav 1980;12:797–801.
24. Vinegar R, Truax JF, Selph JL, Welch RM, White HL. Potentiation of the anti-inflammatory and analgesic activity of aspirin by caffeine in the rat. Proc Soc Exp Biol Med 1976;151:556–60.
25. Sigg EB, Caprio G, Schneider JA. Synergism of amines and antagonism of reserpine to morphine analgesia. Proc Soc Exp Biol Med 1958;97:97–100.
26. Berkowitz BA, Tarver JH, Spector S. Release of norepinephrine in the central nervous system by theophylline and caffeine. Eur J Pharmacol 1970;10:64–71.
27. Waldeck B. Some effects of caffeine and aminophylline on the turnover of catecholamines in the brain. J Pharm Pharmacol 1971;23:824–30.
28. Corrodi H, Fuxe K, Johsson G. Effects of caffeine on central monoamine neurons. J Pharm Pharmacol 1972;24:155–8.
29. Zemlan FP, Corrigan SA, Pfaff DW. Noradrenergic and serotonergic mediation of spinal analgesia mechanisms. Eur J Pharmacol 1980;61:111–24.
30. Watkins LR, Mayer DJ. Organization of endogenous opiate and nonopiate pain control systems. Science 1982;216:1185–92.
31. Fields HL. Neurophysiology of pain and pain modulation. Am J Med 1984;77:2–8.

# Analgetic Contribution of Sufentanil during Halothane Anesthesia:
## A Mechanism Involving Serotonin

John S. Althaus, MS, Edward D. Miller, JR, MD, Jeffrey C. Moscicki, MS, Bernice R. Hecker, MD, and Cosmo A. DiFazio, MD, PhD

ALTHAUS JS, MILLER ED, MOSCICKI JC, HECKER BR, DIFAZIO CA. Analgetic contribution of sufentanil during halothane anesthesia: a mechanism involving serotonin. Anesth Analg 1985;64:857–63.

*Catecholamine and serotonin concentrations in the cord, medulla, and hypothalamus were measured in rats after saline, after sufentanil sufficient to reduce the minimum alveolar concentration (MAC) of halothane by 30% or less, or after sufentanil sufficient to reduce the MAC of halothane by 80% or more. In the cord, high doses of sufentanil resulted in a 13.4% reduction ($P < 0.05$) in serotonin concentration compared to saline control and a 17.4% reduction ($P < 0.05$) in serotonin concentration compared to low dosages of sufentanil. A 12.8% reduction ($P < 0.05$) in medullary serotonin also was observed with high sufentanil compared to low sufentanil. Epinephrine decreased significantly in the hypothalamus at the high sufentanil dose. No other significant differences were found in catecholamine content. The experimental results support the hypothesis that sufentanil may contribute to an analgetic component of general anesthesia by modulating nociception via the release of 5-HT.*

Key Words: ANESTHETICS, VOLATILE—halothane. ANESTHETICS, INTRAVENOUS—sufentanil. BRAIN—serotonin. SEROTONIN—cerebral.

Sufentanil is a substituted derivative of fentanyl that is more potent and less toxic than fentanyl or morphine (1). Recently sufentanil was shown to reduce the minimum alveolar concentration (MAC) of halothane by more than 90% in rats (2).

Evidence suggests that central monoamines may play an important role in the analgetic control of anesthesia, although this has not been clearly elucidated. Yaksh and Tyce showed that microinjections of morphine into the periaqueductal gray (PAG) evoked the release of serotonin from the spinal cord (3). These injections resulted in analgesia that could be reduced by inhibition of 5-HT terminals in the spinal cord (4). Wang showed that the direct intrathecal administration of serotonin resulted in antinociception (5) and mimicked the analgetic effect of morphine injected into the PAG, as reported by Yaksh and Tyce. When the PAG was electrically stimulated in human patients, Newfield et al. (6) found that halothane MAC was reduced by 73%. Ahtee showed that chronic morphine administration decreased 5-HT in rat brains (7). These findings suggest that the ability of narcotics to contribute to an analgetic component of general anesthesia may be related to modulation of nociception by the narcotic activation of 5-HT release in central nervous system tissues. To test this possibility further, we have measured concentrations of monoamines in nervous tissue in three groups of rats. One group, receiving only halothane anesthesia at 1 MAC, was designated as the control. The other two groups were designated as the low-dose and the high-dose sufentanil groups. The proposed mechanism of halothane MAC reduction by narcotics would be supported if our data showed a relationship between increased dosages of sufentanil and decreased levels of 5-HT in central nervous system tissue.

## Methods

Halothane MAC and reductions in halothane MAC were established as reported previously (2). Briefly, 19 Sprague–Dawley rats weighing 250–350 g were anesthetized with halothane and then were intubated. Ventilation was controlled with a Harvard animal respirator. Arterial blood–gas tensions were kept normal throughout each experiment. The femoral artery and vein of the rats were cannulated using PE50 tubing. Heart rate and colonic temperature were mon-

---

Received from the Department of Anesthesiology, University of Virginia Medical Center, Charlottesville, Virginia. Accepted for publication April 23, 1985.

Address correspondence to Dr. DiFazio, Department of Anesthesiology, University of Virginia Medical Center, Box 238, Charlottesville, VA 22908.

© 1985 by the International Anesthesia Research Society

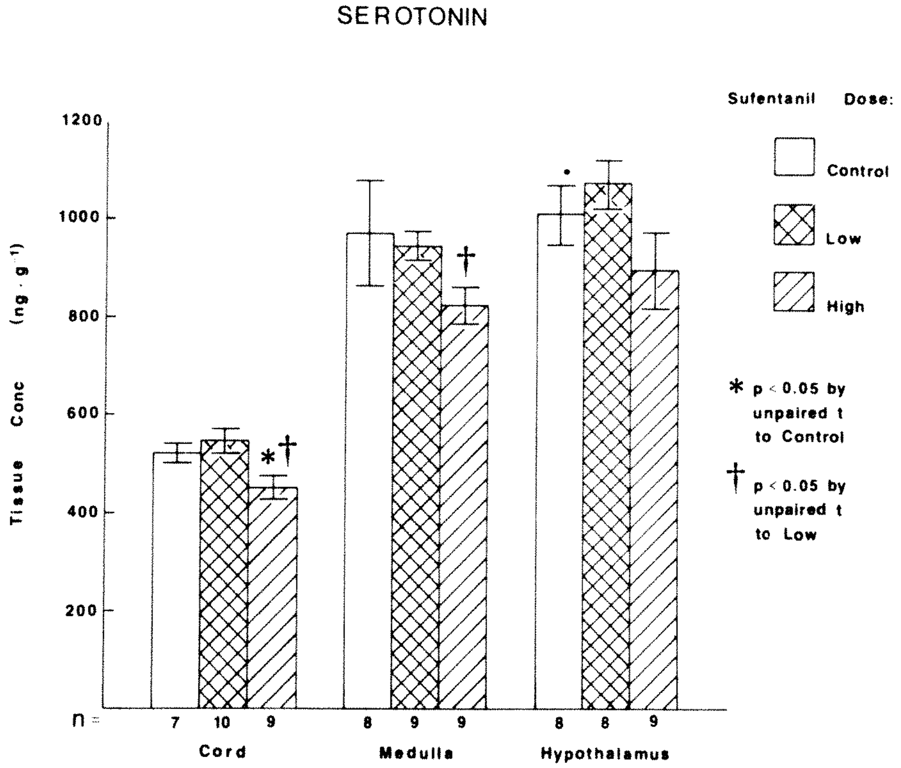


Figure 1. Tissue concentrations of serotonin in the cord, medulla, and hypothalamus of rats treated with no sufentanil (control), sufentanil at 7 × $10^{-5}$ mg·kg$^{-1}$·min$^{-1}$ or less (low) and sufentanil at 1 × $10^{-4}$ mg·kg$^{-1}$·min$^{-1}$ or more (high). Data represent mean values ± SEM.

itored. Alveolar concentrations of halothane were assayed by gas liquid chromatography with flame ionization detection. Halothane MAC in the presence and absence of sufentanil was established according to the method described by Eger et al. (8). MAC was considered to be the point midway between the highest concentration of halothane that produced a positive test and the lowest concentration of halothane that produced a negative test. After an intravenous bolus that was three times the subsequent infusion rate per minute, sufentanil was administered to the rats in doses ranging from $1{\cdot}10^{-7}$mg·kg$^{-1}$ ·min$^{-1}$ to $1{\cdot}10^{-3}$mg·kg$^{-1}$·min$^{-1}$ by continuous infusion. Monoamines were measured in the brains of three groups of rats. One group, receiving 1 MAC of halothane (vol% 0.74 ± 0.06), was designated the control. The other two groups were determined based on a dose–response curve relating percent halothane MAC reduction to the infusion of increasing concentrations of sufentanil (2). Nine rats associated with data located above the inflection point of the curve ($\geq 1{\cdot}10^{-4}$mg·kg$^{-1}$·min$^{-1}$ yielding 80% MAC reduction or greater) were grouped together and are referred to as the high-dose sufentanil group. Ten rats associated with data located below the inflection point of the curve ($\leq 7{\cdot}10^{-5}$mg·kg$^{-1}$·min$^{-1}$ yielding 30% MAC reduction or less) were grouped together and are referred to as the low-dose sufentanil group.

Immediately after the conclusion of each experiment, anesthetized rats were given a slow intravenous 1-ml injection of 5% $Na_2$ EDTA in saline to control chemical and enzymatic breakdown of bioamines. The spinal cord was then severed above the fifth vertebra, and the brain and cord were removed intact and chilled. The cord was sectioned away from the medulla, and the medulla and hypothalamus were dissected according to the guidelines of Glowinski et al. (9). Tissues were then frozen at −80°C and stored for subsequent analysis.

Tissues were weighed and added to test tubes containing 1 ml of an extraction solution composed of 75% ethanol containing *n*-methyl serotonin, an internal standard for 5-HT, and dihydroxybenzylamine, an internal standard for catecholamines. Samples were homogenized using a Brinkman polytron and centrifuged. A 200-μl aliquot of the supernatant was obtained for determination of 5-HT content. One ml of 0.1 N perchloric acid was added back to the pellet, mixed with the supernatant remaining, and centrifuged. The supernatant from this step was decanted and used for the determination of catecholamine content.

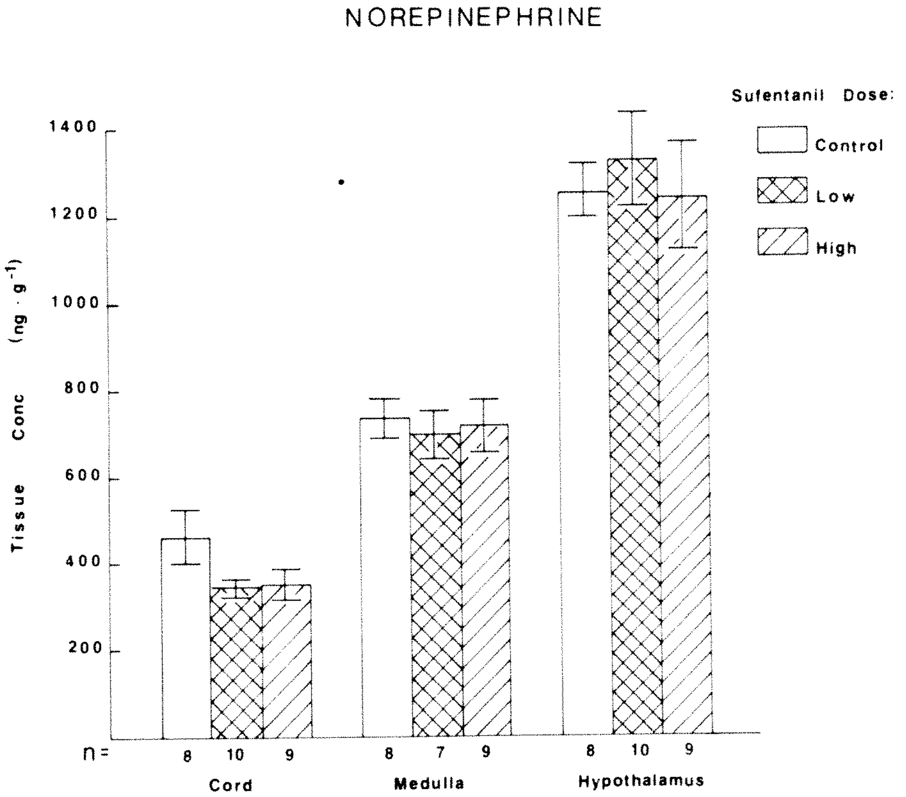


Figure 2. Tissue concentrations of norepinephrine in the cord, medulla, and hypothalamus of rats treated with no sufentanil (control), sufentanil at 7 × $10^{-5}$ mg·kg$^{-1}$·min$^{-1}$ or less (low) and sufentanil at 1 × $10^{-4}$ mg·kg$^{-1}$·min$^{-1}$ or more (high). Data represent mean values ± SEM. No significant differences were observed.

Serotonin was asssayed by high-performance liquid chromatography (HPLC) after a modified procedure of Lyness et al. (10). Briefly, the ethanolic brain extract was loaded onto a small column containing Bio-Rad cation exchange resin. The resin was washed with 0.02 M phosphate buffer, washed with distilled $H_2O$, and eluted with 2 M $(NH_4)_2SO_4$ to deadsorb 5HT. A 200-μl aliquot of the eluate was injected onto an octadecylsilane (ODS) column. Serotonin and its internal standard were resolved and detected electrochemically with a 50-pg sensitivity threshold. The mobile phase was composed of $Na_2EDTA$ (400 mg·L$^{-1}$), monochloroacetate (9.45 g·L$^{-1}$), acetonitrile (70 ml·L$^{-1}$) and alkalinized to pH 3 with NaOH. The flow rate was 2 ml·L$^{-1}$.

Catecholamines were assayed by HPLC after the procedure of Woodside et al. (11). Briefly, the perchloric acid extract was alkalized to pH 8.6, and catecholamines were adsorbed to alumina. The alumina was washed with distilled water and catecholamines eluted with 200 μl of 0.1 N perchloric acid. This eluate was injected and separated by a 5-μm ODS column. Catecholamines were detected electrochemically with a 30-pg sensitivity threshold. The mobile phase was composed of sodium octylsulfate (660 mg·L$^{-1}$), $Na_2EDTA$ (400 mg·L$^{-1}$), monochloroacetate (9.45 g·L$^{-1}$), acetonitrile (70 ml·L$^{-1}$) and alkalinized to pH 3 with NaOH. The flow rate was 1 ml·min$^{-1}$.

Mean values ± standard error of the mean (SEM) were calculated. Statistical differences were determined using the two-sample *t*-test, where $P < 0.05$ was considered significant.

## Results

Tissue levels of serotonin in the cord, medulla, and hypothalamus were compared (Fig. 1) in control rats and in rats given two different doses of sufentanil. In the cord, high doses of sufentanil resulted in a significant ($P = 0.047$) 13.4% reduction in serotonin levels below levels observed in the control group and a significant ($P = 0.018$) 17.4% reduction in serotonin below levels observed after low doses of sufentanil. The difference between cord levels of serotonin in the control group and in the low-dose sufentanil group was not statistically significant. In the medulla and hypothalamus, the serotonin levels tended to change in the same way as in the cord, but only the 12.8% difference between low- and high-dose groups in the medulla was significant ($P = 0.020$). Levels of norepinephrine (NE) and dopamine (DA) in the cord, medulla, and hypothalamus were not significantly

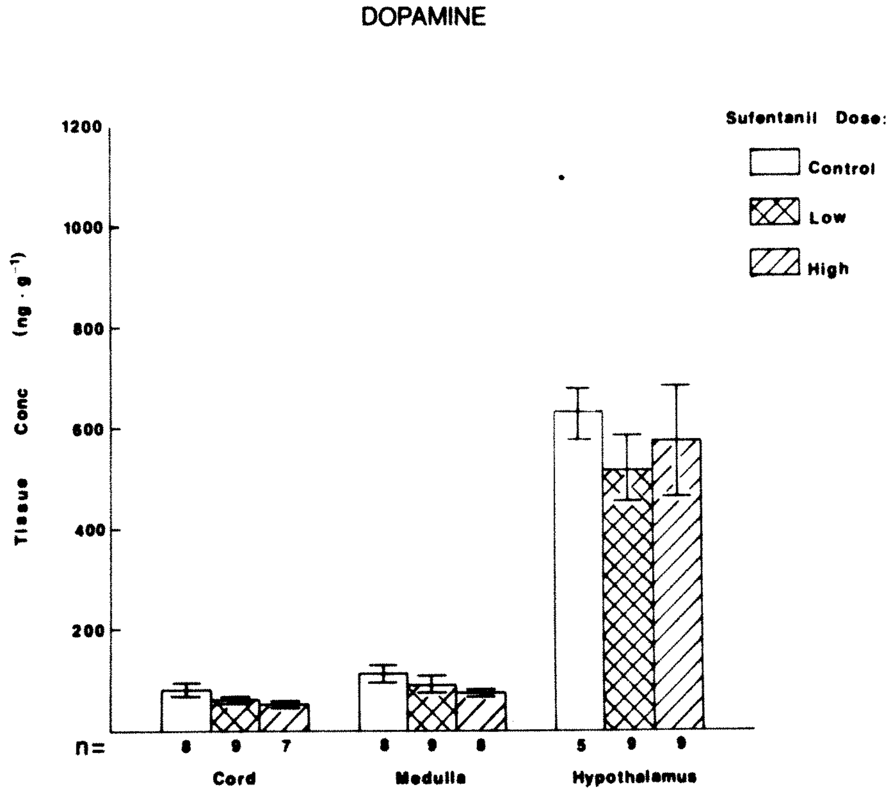


Figure 3. Tissue concentrations of dopamine in the cord, medulla, and hypothalamus of rats treated with no sufentanil (control), sufentanil at $7 \times 10^{-5}$ $mg \cdot kg^{-1} \cdot min^{-1}$ or less (low) and sufentanil at $1 \times 10^{-4}$ $mg \cdot kg^{-1} \cdot min^{-1}$ or more (high). Data represent mean values ± SEM.

different for any of the three groups (Figs. 2, 3). There also were no significant differences in cord or medullary epinephrine levels (Fig. 4), but in the hypothalamus a significant ($P = 0.004$) reduction in epinephrine was found when comparing the high-dose sufentanil group to the control group.

## Discussion

The anesthetic action of halothane has been studied in terms of monoamine changes in brain tissues. Diaz et al. (12) found that 0.75% halothane resulted in a 10% decrease in rat cerebral 5-HT after 2 hr. Conversely, Roizen et al. (13), using a microdissection technique on the rat brain, showed increased 5-HT in the nuclear amygdaloideus centralis, substantia nigra, and nucleus centralis superior after about 90 min of exposure to 1% halothane. Similar halothane concentrations were reported by Ngai et al. (14) to increase NE in rat whole brain and by Roizen et al. (15) to increase NE and DA in discrete rat brain regions. Berl et al. (16), however, demonstrated that clinical levels of halothane facilitated release of radiolabeled NE from synaptosomes prepared from rat brain. We have confirmed this by measuring endogenous release of NE from synaptosomes (17). Furthermore, our results also were associated with decreased intracellular NE content. The interpretation of these results is difficult, but more importantly, as Roizen et al. stated (13), changes in levels of transmitter do not establish a cause and effect relationship.

In order to understand causality, one approach has been to alter central monoamine content pharmacologically or surgically, followed by an assessment of the effect on anesthetic potency. In general, drugs that produce global depletion of monoamines cause a decrease in the anesthetic requirement of halothane (18,19). Specifically, Mueller et al. (18) found that the decrease in halothane MAC (10–27%) was small compared to extensive depletion of central monoamines (50–86%) after drug treatment. Roizen et al. (20) effected more pronounced decreases in halothane MAC (31–35%) by specific brain lesions of the locus ceruleus, nucleus raphe dorsalis, and ventral bundle. These lesions resulted in extensive depletion (75–86%) of cortical NE and 5-HT, as well as hypothalamic NE. Even though specific monoamine ablation of brainstem regions resulted in greater MAC reduction than global monoamine depletion by drugs, the treatment was far less effective in reducing MAC than sufentanil administration. In one study, sufentanil doses of $10^{-3} mg \cdot kg^{-1} \cdot min^{-1}$ reduced MAC in some cases by more than 90% but (2) were associated with only a small 5-HT depletion of 17% or less. Unlike the studies above showing extensive 5-HT depletion resulting in small reductions in halothane MAC, we observed far

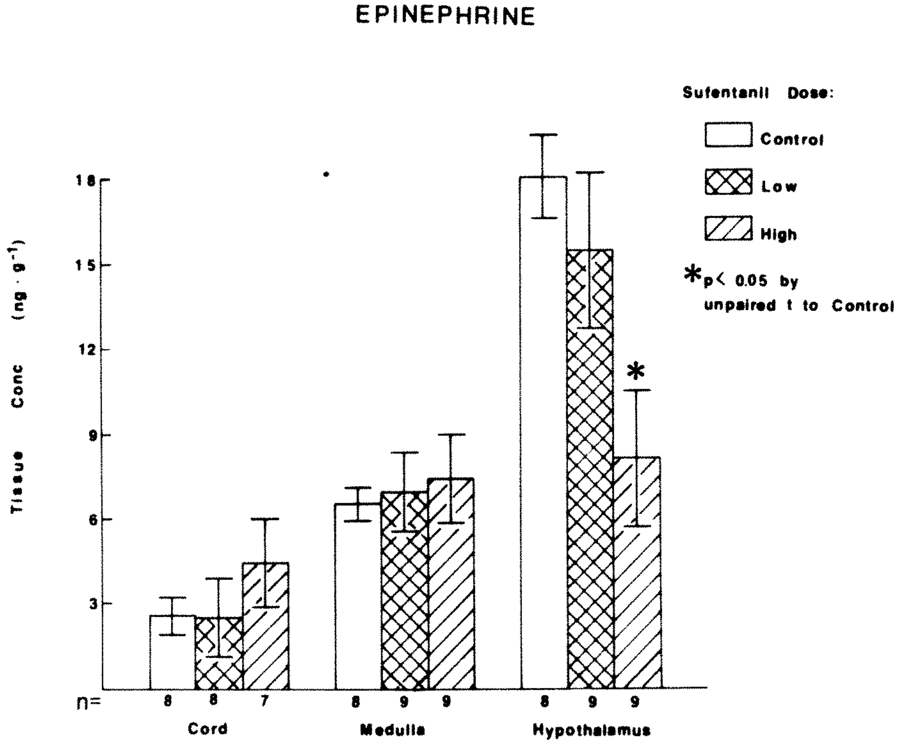


Figure 4. Tissue concentrations of epinephrine in the cord, medulla, and hypothalamus of rats treated with no sufentanil (control), sufentanil at $7 \times 10^{-5}$ mg·kg$^{-1}$·min$^{-1}$ or less (low) and sufentanil at $1 \times 10^{-4}$ mg·kg$^{-1}$·min$^{-1}$ or more (high). Data represent mean values ± SEM. A significant decrease in epinephrine was observed in the hypothalamus in those rats treated with high-dose sufentanil.

less 5-HT depletion associated with much greater reductions in halothane MAC with sufentanil. This finding suggests that the sufentanil-dependent depletion of central 5-HT alone was not the primary cause of MAC reduction observed in our experiments. Instead, a more plausible explanation is that MAC reduction with sufentanil resulted from a narcotic-dependent increase in 5-HT release as previously noted (3–5). The small but significant depletion of 5-HT was an important indicator of a release process having taken place.

The assumption that 5-HT depletion resulted from increased release is justified if the rates of synthesis and of reuptake are less than the rate of release. Evidence for this set of circumstances is suggested by several studies dealing with 5-HT turnover and uptake. Vasko and Vogt (21) showed that in rats made tolerant to morphine, the systemic administration of additional morphine resulted in a profound increase in resistance to pain, a significant increase in cord 5-HT turnover, but no decrease in cord 5-HT. There are at least three possible reasons why cord 5-HT was significantly decreased with sufentanil in our study but not significantly decreased with morphine in the Vasko and Vogt study. First, sufentanil is more potent than morphine (1); second, our HPLC-electrochemical assay is more sensitive than the fluorometric assay used by Vasko and Vogt (21); and third, halothane may potentiate the depletion of serotonin. The third possibility is based on a report by Berl et al. showing that, in synaptosomes, halothane inhibited the high affinity uptake of 5-HT (16). In vivo, if the reuptake of 5-HT were inhibited by halothane, then a portion of 5-HT supplied to cellular stores by this route would be depleted. This prediction was demonstrated in rats by Diaz et al. (12), who reported a small but significant decrease in cerebral 5-HT after a 2-hr exposure to 0.75% halothane. In our experiments, rats were exposed to halothane at 1 MAC for about 30 min prior to drug treatment and, therefore, any direct effects on 5-HT depletion would be small and evenly distributed between groups. Nevertheless, if 5-HT release was stimulated by a narcotic such as sufentanil in the presence of an uptake inhibitor such as halothane, then depletion of 5-HT would be expected to be potentiated. Under these conditions 5-HT depletion also would be technically more readily demonstrable.

The authors recognize that there may very likely exist more than one possible mechanism for the analgetic effects of narcotics. In a recent review (23), Cousins and Mather point out that nociception may be regulated by input from GABA, glycine, norepinephrine, and opioid-containing neurons, as well as others not yet clearly identified. Roizen et al. emphasized that anesthetic potency also may depend on the function of specific brainstem nuclei (20). Narcotics may selectively alter these nuclei or nerve tracts, thereby bringing about reductions in anesthetic potency. It is also known that 5-HT receptors are associated with both excitatory and inhibitory cellular responses (24). Given this high level of complexity, our results, nevertheless, support a significant role played by 5-HT when halothane MAC is reduced by sufentanil.

We have shown that high doses of sufentanil ($>1 \times 10^{-4}$ mg·kg$^{-1}$·min$^{-1}$) produced reductions in halothane MAC by 80% or more and also produced a reduction of serotonin in the cord and possibly the medulla. It was not unexpected that the low-dose sufentanil group was not significantly different from the control and therefore did not give a distinct dose-related depletion of 5-HT measured in central nervous system (CNS) tissues. There may very likely exist more than one possible mechanism for the analgetic effects of sufentanil. At low concentrations of sufentanil, the observed reduction in MAC may proceed by a mechanism that does not involve serotonin. It may be that only at high doses are the effects of 5-HT observed. Alternatively, it may be that an increased rate of 5-HT release with sufentanil exceeds the rate of synthesis of 5-HT only at high doses of sufentanil and not at low doses of sufentanil. In either case, the data show a positive correlation between increased doses of sufentanil and decreased levels of 5-HT in several CNS tissues.

Except for hypothalamic epinephrine, the effect of sufentanil on central monoamine concentrations appeared to be limited to serotonin. The significance of the reduction in the hypothalamic concentrations of epinephrine below control levels when high doses of sufentanil were given is unknown. Endogenous epinephrine function has not yet been shown to be a modulator of nociception. The change in epinephrine may have occurred because some other facet of opioid regulation was functioning, such as hemodynamic or cardiovascular control (25). Primarily, the present study showed a relationship between the anesthetic potency of sufentanil and the reduction of serotonin in CNS tissue, particularly in the cord. This result is consistent with the proposition that sufentanil may contribute to an analgetic component of general anesthesia by modulating 5-HT release. Release then produces antinociception and may result in a depletion of 5-HT in CNS tissues.

## References

1. Niemegeers CJE, Schellekens KHL, Van Bever WFM, Janssen PAJ. Sufentanil a very potent and extremely safe intravenous morphine-like compound in mice, rats and dogs. Avzneum Forsch/Drug Res 1976;26:1551–6.
2. Hecker BR, Lake CL, DiFazio CA, Moscicki JC, Engle JS. The decrease of the minimum alveolar anesthetic concentration produced by sufentanil in rats. Anesth Analg 1983;62:987–90.
3. Yaksh TL, Tyce GM. Microinjection of morphine into the periaqueductal gray evokes the release of serotonin from spinal cord. Brain Res 1979;171:176–81.
4. Yaksh TL. Direct evidence that spinal serotonin and noradrenaline terminals mediate the spinal antinociceptive effects of morphine in the periaqueductal gray. Brain Res 1979;160:180–5.
5. Wang JK. Antinociceptive effects of intrathecally administered serotonin. Anesthesiology 1977;47:269–71.
6. Newfield P, Roizen MF, Hosobuchi Y, Eger EI II, Adams JE, Lamb S. Stimulation of the periaqueductal gray area reduces anesthetic requirement. Anesthesiology 1980;53:S16.
7. Ahtee L. Chronic morphine administration decreases 5-hydroxytryptamine and 5-hydroxyindoleacetic acid content in the brain of rats. Med Biol 1980;58:38–44.
8. Eger EI II, Saidman LJ, Bandstater B. Minimum alveolar anesthetic concentration: a standard of anesthetic potency. Anesthesiology 1965;26:756–63.
9. Glowinski J, Iversen LL. Regional studies of catecholamines in the rat brain-I. J Neurochem 1966;13:655–69.
10. Lyness WH, Friedle NM, Moore KE. Measurement of 5-hydroxytryptamine acid in decrete brain nuclei using reverse phase liquid chromatography with electrochemical detection. Life Sci 1980;26:1109–14.
11. Woodside JR, Beckman JJ, Althaus JS, Peach JM, Longnecker DE, Miller ED. Renovascular hypertension: effects of halothane and enflurane. Anesthesiology 1984;60:440–7.
12. Diaz PM, Ngai SH, Costa E. The effects of cyclopropane, halothane and diethyl ether on the cerebral metabolism of serotonin in the rat. Anesthesiology 1968;29:959–63.
13. Roizen MF, Kopin IJ, Palkovits M, Brownstein M, Kizer JS, Jacobowitz PM. The effect of two diverse inhalation anesthetic agents on serotonin in discrete regions of the rat brain. Exp Brain Res 1975;24:203–7.
14. Ngai SH, Neff NH, Cost E. The effects of cyclopropane and halothane on the biosynthesis of norepinephrine in vivo: conversion of $^{14}$C-tyrosine to catecholamines. Anesthesiology 1969;31:53–60.
15. Roizen MF, Kopin IJ, Thoa NB, Zivin J, Muth EA, Jacobowitz DM. The effect of two anesthetic agents on norepinephrine and dopamine in discrete brain nuclei, fiber tracts, and terminal regions of the rat. Brain Res 1976;110:515–22.
16. Berl S, Getzow JJ, Nicklas WJ, Mahendran C. Effect of halogenated hydrocarbons on synaptosomal uptake and release of neurotransmitters. Prog Clin Biol Res 1979;27:135–49.
17. Taylor SP, Althaus JS, Lynch C III. Halothane and verapamil effects on catecholamine release in the central nervous system. Anesthesiology 1984;61:A358.
18. Mueller RA, Smith RD, Spruill WA, Breese GR. Central monoaminergic neuronal effects on minimum alveolar concentrations (MAC) of halothane and cyclopropane in rats. Anesthesiology 1975;42:143–52.
19. Johnston RR, Way WL, Miller RD. The effects of CNS catecholamine-depleting drugs on dextroamphetamine-induced elevation of halothane MAC. Anesthesiology 1974;41:57–61.
20. Roizen MF, White PF, Eger EI II, Brownstein M. Effects of ablation of serotonin or norepinephrine brain-stem areas on halothane and cyclopropane MACs in rats. Anesthesiology 1978;49:252–5.
21. Vasko MR, Vogt M. Analgesia, development of tolerance, and

5-hydroxytryptamine turnover in the rat after cerebral and systemic administration of morphine. Neuroscience 1982;7:1215–25.

22. Cross AJ, Joseph MH. The concurrent estimation of the major metabolites in human and non-human primate brain by HPLC with fluorescence and electrochemical detection. Life Sci 1981;28:499–506.
23. Cousins MJ, Mather LE. Intrathecal and epidural administration of opioids. Anesthesiology 1984;61:276–310.
24. Jalfre M, Ruch-Monachon MA, Haefely W. Methods for assessing the interaction of agents with 5-hydroxytryptamine neurons and receptors in the brain. Adv Biochem Psychopharmacol 1974;10:121–34.
25. Fuxe K, Bohne P, Jonsson G, Agnati LF, Goldstein M, Hokfelt T, Schwarcz R, Engle J. On the cardiovascular role of noradrenalin, adrenalin and peptide containing neuron systems in the brain. Perspect Nephrol Hypertens 1979;10:1–7.

ANESTH ANALG
1985;64:864–6

# Response Differences of Paretic and Healthy Extremities to Pancuronium and Neostigmine in Hemiplegic Patients

Hiroshi Iwasaki, MD, Akiyoshi Namiki, MD, Keiichi Omote, MD, Tetsuo Omote, MD, and Takeo Takahashi, MD

IWASAKI H, NAMIKI A, OMOTE K, OMOTE T, TAKAHASHI T. Response differences of paretic and healthy extremities to pancuronium and neostigmine in hemiplegic patients. Anesth Analg 1985;64:864–6.

*The purpose of this study was to examine differences in train-of-four (TOF) ratios between paretic and healthy extremities after pancuronium and neostigmine administration in 31 patients with hemiparesis. The TOF ratios on the paretic side after pancuronium administration were greater than those on the healthy side in all patients. Patients were classified according to the size of the difference in the TOF ratio on both sides. In group 1, differences in TOF ratios were greater than 20%, and in group 2, they were less than 20%. Fifteen of 17 patients in group 1 had hemiparesis for over three weeks, and in group 2, 10 of 14 patients had hemiparesis for less than three weeks. Patients with flaccid hemiparesis were distributed equally in both groups, while all patients with spastic hemiparesis belonged to group 1. The difference in increase in TOF ratios after neostigmine was the same as the difference in decrease produced by pancuronium.*

Key Words: NEUROMUSCULAR RELAXANTS—pancuronium. COMPLICATIONS—paraplegia.

Monitoring of train-of-four (TOF) ratios is routine during the administration of muscle relaxants. TOF monitoring in hemiparetic patients, however, may be an unreliable guide for determining the dosage of nondepolarizing muscle relaxants and their antagonists because the TOF ratio on the paretic extremity differs from that on the healthy side (1,2). The purpose of this study was to investigate TOF ratio differences in the paretic and healthy extremities after intravenous administration of pancuronium and neostigmine. Factors considered were duration, type, and degree of muscle weakness in hemiparesis.

## Materials and Methods

The subjects, 31 hemiparetic patients undergoing elective surgery, ranged in age from 28 to 66 yr (average 47.2 yr); 21 were males, 10 females. The causes of hemiparesis were cerebrovascular in 28 and cerebral tumor in three patients. The study was approved by the Ethical Committee of Sapporo Medical College and Hospital, and informed consent was obtained from each patient. All patients were free from hepatic or renal disease. The duration of hemiparesis ranged from 4 hr to 8 yr, and the grade of muscle weakness varied from nearly complete recovery with minimal residual weakness to a complete hemiplegia. The hemiparesis was flaccid in 28 and spastic in three patients.

All patients were premedicated with intramuscular hydroxyzine, 100 mg, and atropine, 0.5 mg, 1 hr preoperatively. Anesthesia, induced by thiamylal, 200–300 mg intravenously, was maintained with 60–70% nitrous oxide in oxygen administered by a face mask. The TOF responses of both upper extremities were recorded simultaneously while the dosage of pancuronium was gradually increased based upon TOF ratios measured on the healthy side.

The TOF ratios were measured by the method of Ali et al. (3). The forearm and hand of the patient were fixed to an armboard, and a force-displacement transducer was attached to the thumb. The ulnar nerve was stimulated at the wrist with subcutaneous needle electrodes using a square-wave, supra-maximal stimulus of 0.2 msec duration at the rate of 2 Hz. The isometric twitch tension of the indirectly stimulated adductor muscle was recorded, and the TOF ratio was automatically calculated (Myograph-2000, Biometer, Denmark). The resting tension applied to the thumb during the study was adjusted to 200 g.

After TOF responses were studied, the trachea was intubated and halothane, 0.5–1.0%, was added to maintain anesthesia intraoperatively. At the conclusion of surgery, the reversal effect of neuromuscular

---

Received from the Department of Anesthesiology, Sapporo Medical College and Hospital, Chuoku, Sapporo, Japan. Accepted for publication April 4, 1985.

Address correspondence to Dr. Iwasaki, Department of Anesthesiology, Sapporo Medical College and Hospital, South 1, West 16, Chuoku, Sapporo, 060, Japan.

blockade with neostigmine was observed on the paretic and healthy extremities in 16 patients. Statistical analysis was performed using a Student's *t*-test or $\chi^2$-test.

## Results

The decrease in the TOF ratios after pancuronium administration is illustrated in Figure 1. After intravenous administration of pancuronium, the TOF ratios on the paretic side were always greater than those on the healthy side. Thirty-one patients were divided into two groups according to the magnitude of difference in the TOF ratios between the paretic and healthy sides. In group 1 (17 patients), the difference in TOF ratios between both sides was greater than 20%. On the other hand, in group 2 (14 patients), the difference in TOF ratios never exceeded 20%.

There were no significant differences between the groups in sex, age or weight. The duration, degree of muscle weakness, and the type of hemiparesis in both groups are summarized in Table 1. Fifteen of 19 patients who had hemiparesis for more than three weeks belonged to group 1, and 10 of 12 patients whose hemiparesis was present less than three weeks belonged to group 2. All four patients who had been hemiparetic for less than a day were in group 2. The number of patients with severe to moderate muscle weakness was greater in group 1 than group 2. However, there were no statistically significant differences in the grade of muscle weakness between the groups. Twenty-eight patients had flaccid hemiparesis, and these patients were divided equally between both groups. Three patients with spastic hemiparesis belonged to group 1.

Figure 2 shows the decrease in TOF ratios after pancuronium administration and recovery of the TOF ratio after neostigmine administration to the same patients in both groups. The TOF ratios on the paretic side were plotted at 70, 50, and 30% of the ratios on the healthy side, respectively. The TOF ratios on both paretic and healthy sides produced by pancuronium were reversed by neostigmine in the same way that they were initially affected by pancuronium.

## Discussion

This study confirms that a paretic extremity is consistently resistant to a nondepolarizing muscle relaxant, pancuronium, in hemiparetic patients with upper motor neuron lesions. The difference in TOF on the hemiparetic and on the healthy sides after pancuronium was evident even in four patients experiencing hemiparesis for only one day.

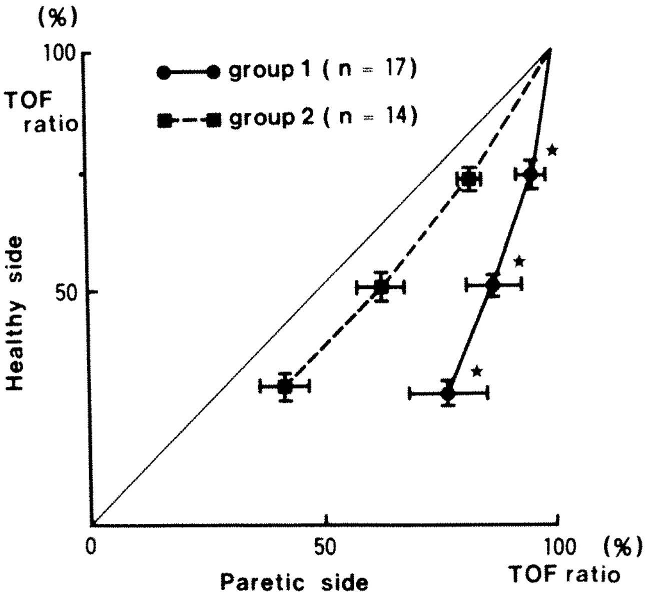


Figure 1. The courses of decay of the train-of-four (TOF) ratios after pancuronium bromide administration.

Although the cause of response differences to nondepolarizing relaxants among hemiparetic extremities remains to be fully defined, it is thought that an increase in extrajunctional acetylcholine receptors on the paretic side may be a factor in explaining the resistance to nondepolarizing neuromuscular blockade (1). Acetylcholine receptors (ACh-R) in normally innervated muscles are more dense at neuromuscular junctions than in extrajunctional areas. In denervated or disused muscles, however, extrajunctional ACh-R density increases markedly due to a spread of receptor sites into extrajunctional areas beyond the neuromuscular junction (4,5). The presence of extrajunctional ACh-R is suggested to be important to the formation of a new synaptic connection between motor neurons and skeletal muscle fibers (6).

We know there is a close relationship between the degree of muscle denervation and the level of motor nerve sprouting (7). The increase of extrajunctional ACh-R is greater in denervated muscle than in partially denervated or disused muscles (4,8). We, therefore, thought that severe muscle weakness in hemiparetic patients would be associated with a great difference in TOF ratios between the intact and paralyzed extremities. However, in our study, no significant correlation was found between differences in TOF ratios on the two sides and the degree of muscle weakness. Receptors of extrajunctional sites have almost the same binding properties for nondepolarizing relaxants as do junctional receptors (5,6). Therefore, in the denervated or disused muscle it is likely

Table 1. Relationship Between the Differences in Train-of-Four Ratios and the Duration of Hemiparesis, Grade of Muscle Weakness, and Type of Hemiparesis

| | Duration of hemiparesis | | | | | Grade of muscle weakness[1] | | | Type of hemiparesis | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0-1W | 1-3W | 3W-3M | 3M-1Y | 1Y-8Y | Severe | Moderate | Slight | Spastic | Flaccid |
| Group 1 (*n* = 17) | 0 | 2 | 7 | 6 | 2 | 8 | 6 | 3 | 3 | 14 |
| Group 2 (*n* = 14) | 6 | 4 | 2 | 1 | 1 | 6 | 2 | 6 | 0 | 14 |

[1] Grades of muscle weakness: severe, hemiplegia or inability to raise extended leg; moderate, able to raise extended leg but with reduced muscle power; slight, nearly complete recovery of function.

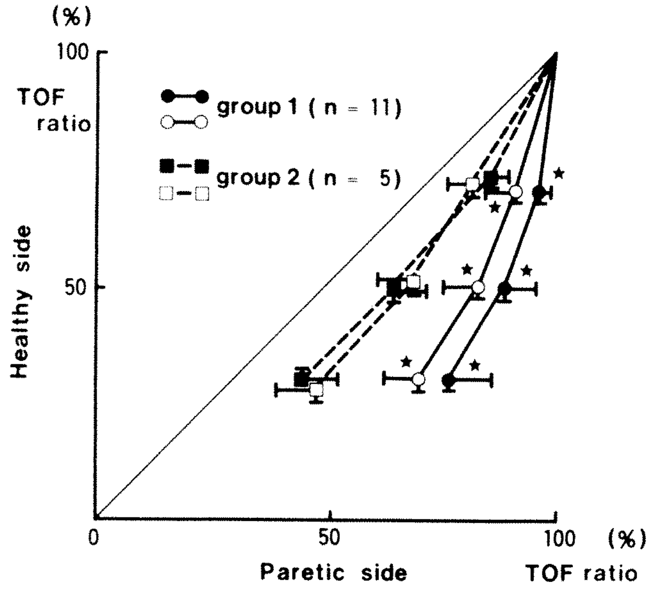


Figure 2. The courses of decay of the train-of-four (TOF) ratios after pancuronium bromide and neostigmine administration in the same patients. Symbols: filled circles of Group 1 and filled squares of Group 2 represent the TOF ratios after pancuronium administration; the open circles and open squares represent the TOF ratios after neostigmine administration. All values are mean ± SD. ★$P <$ 0.01 vs Group 2.

that more of the nondepolarizing relaxant would be found in extrajunctional areas (5).

The number of ACh-R sites begins to increase about two days after denervation, peaks 1–3 weeks later, and then slowly declines (6). However, it is known that sprouting of the motor nerve starts at a submicroscopic level about one day after denervation (8). This might explain why the difference in TOF ratios tended to be smaller in patients who had paresis for less than three weeks and larger in those who had paresis for more than three weeks, even though a difference in TOF ratios between the paretic and healthy side was observed in four patients with hemiparesis for only 4–8 hr. The appearance of resistance to nondepolarizing muscle relaxants within 4–8 hours in hemiparetic patients cannot be explained sufficiently.

All three of our patients with spastic hemiparesis showed a large difference in TOF ratios on the two sides, although it has been reported that patients with spastic paraplegia due to spinal cord disorders are hypersensitive to curare (9). Changes in TOF ratios after neostigmine administration indicated that muscular blockade on both the paretic and healthy sides after pancuronium administration was reversed, with the same differences as those observed at the onset of neuromuscular blockade produced by pancuronium. This indicates that the paretic extremity is resistant to neostigmine as well as to pancuronium.

In conclusion, nondepolarizing muscle relaxants and the reversal drugs have different effects on paretic and healthy extremities. Therefore, when these drugs are administrated, the TOF ratio on the healthy side of hemiparetic patients should be monitored to determine accurately the degree of neuromuscular blockade.

## References

1. Moorthy SS, Hilgenberg JC. Resistance to non-depolarizing muscle relaxants in paretic upper extremities of patients with residual hemiplegia. Anesth Analg 1980;59:624–7.
2. Graham DH. Monitoring neuromuscular block may be unreliable in patients with upper-motor-neuron leisions. Anesthesiology 1980;42:74–5.
3. Ali HH, Utting JE, Gray C. Stimulus frequency in the detection of neuromuscular block in humans. Br J Anaesth 1970;42:967–77.
4. Pestronk A, Drachman DB, Griffing JW. Effect of muscle disuse on acetylcholine receptor. Nature 1976;26:352–3.
5. Gronert GA. Disuse atrophy with resistance to pancuronium. Anesthesiology 1981;55:547–9.
6. Fambrough DM. Control of acetylcholine receptors in skeletal muscle. Physiol Rev 1979;59:165–227.
7. Pestronk A, Drachman DB. Motor nerve sprouting and acetylcholine receptors. Science 1978;199:1223–5.
8. Brown MC, Ironton R. Sprouting and regression of neuromuscular synapses in partially denerved mammalian muscles. J Physiol 1978;278:325–48.
9. Brown JC, Charlton JE. Study of sensitivity to curare in certain neurological disorders using a regional technique. J Neurol Neurosurg Psychiatry 1975;38:34–45.

ANESTH ANALG
1985;64:867–70

# A Comparison of Edrophonium and Neostigmine for the Antagonism of Atracurium-Induced Neuromuscular Block

Gavin G. Lavery, FFARCS, Rajinder K. Mirakhur, MD, and Fiona M. Gibson, FFARCS

LAVERY GG, MIRAKHUR RK, GIBSON FM. A comparison of edrophonium and neostigmine for the antagonism of atracurium-induced neuromuscular block. Anesth Analg 1985;64:867–70.

*Edrophonium, 0.5 mg/kg, or neostigmine, 0.05 mg/kg, was administered to groups of 20 patients each, for antagonism of atracurium-induced block at varying degrees of spontaneous recovery. Neuromuscular block was studied using train-of-four (TOF) stimulation. Adequate reversal of neuromuscular block (TOF ratio of 0.7) was achieved in all patients given neostigmine but only in 13 of the 20 given edrophonium. The onset of action of edrophonium (23 sec) was significantly more rapid than that of neostigmine (40 sec), as was the time taken to attain a TOF ratio of 0.7 in those in whom adequate antagonism was achieved (68 sec for edrophonium and 246 sec for neostigmine). Five of the seven patients in the edrophonium group who failed to be reversed adequately had shown three or fewer twitches to a TOF stimulation. It is concluded that edrophonium in a dose of 0.5 mg/kg does not consistently antagonize neuromuscular blockade induced by atracurium, particularly if all four responses to a TOF stimulation are not elicited prior to antagonism of the block.*

Key Words: NEUROMUSCULAR RELAXANTS—atracurium. ANTAGONISTS, NEUROMUSCULAR RELAXANTS—edrophonium, neostigmine.

It traditionally has been believed that edrophonium is ineffective and too short-acting for the antagonism of nondepolarizing neuromuscular block (1,2). This is true when it is administered in doses of approximately 10 mg. However, when administered in doses of 0.5 mg/kg or more, antagonism has been shown to be both effective and sustained (3–5). This is further supported by the pharmacokinetic studies carried out using these doses of edrophonium (6). The main advantages of edrophonium are its rapid onset of action and less marked muscarinic side effects. Thus when it is used, less atropine is required (5,7,8).

More recent studies involving small numbers of patients have indicated that antagonism of atracurium-induced block is better with edrophonium than with neostigmine (9,10). In these studies, antagonism was usually carried out under strict conditions, such as administration of only a single dose of atracurium, 0.25 mg/kg, in the study of Jones et al. (10), and prior spontaneous recovery of block to at least 20% of control in the study by Baird and Kerr (9). Such conditions are not often encountered in routine anesthetic practice. In the present study, we have employed edrophonium for antagonism of atracurium-induced block at the end of surgery irrespective of the degree of block present, and we have compared the results with neostigmine given under similar conditions.

## Methods

Forty ASA grade I patients scheduled for elective ophthalmic surgery were studied. We obtained their informed consent and the approval of the Regional Ethical Committee.

One hr after administration of diazepam, 10 mg, orally, anesthesia, was induced with thiopental and maintained with nitrous oxide, oxygen, fentanyl (2–3 μg/kg), and halothane (0.5–1.0%). Ventilation was adjusted to maintain end-tidal carbon dioxide concentration between 4.5–5.0%. The ulnar nerve was stimulated percutaneously at the wrist with square wave supramaximal stimuli of 0.2 msec duration, delivered in a train-of-four sequence (TOF), at 2 Hz every 10 sec. The resultant contraction of adductor pollicis was recorded using a force displacement transducer and a neuromuscular function analyzer (Myograph 2000, Bio Meter Ltd) (11).

Atracurium was administered in an initial dose of 0.5 mg/kg, and tracheal intubation was performed at maximum block. Further increments of the relaxant

---

Dr. Lavery and Dr. Gibson were supported by Research Fellowships from the Gifts and Endowments Fund, Royal Victoria Hospital, Belfast, Northern Ireland.

Received from the Departments of Clinical Anaesthesia, Royal Victoria Hospital; and The Queen's University, Belfast, Northern Ireland. Accepted for publication March 25, 1985.

Address correspondence to Dr. Mirakhur, Department of Clinical Anaesthesia, Royal Victoria Hospital, Grosvenor Road, Belfast BT12 6BA, N Ireland.

© 1985 by the International Anesthesia Research Society

Table 1. Comparability of the Groups

| | Edrophonium | Neostigmine |
|---|---|---|
| Age (yr ± SEM) | 43 ± 4.1 | 42 ± 4.2 |
| Weight (kg ± SEM) | 63 ± 2.4 | 70 ± 2.6 |
| T1 prior to antagonism (%) | 36 ± 4.5 | 33 ± 4.7 |
| TOF ratio prior to antagonism | 0.22 ± 0.037 | 0.21 ± 0.027 |

were given as required. Heart rate and rhythm and arterial blood pressure were monitored throughout with an electrocardiogram and an oscillotonometer (Dinamap, Critikon Ltd).

At the end of surgery, antagonism of residual block was attempted provided at least one response was evoked by a TOF stimulation. Halothane was discontinued about 10 min before attempted reversal. Patients were randomly allocated to receive either edrophonium, 0.5 mg/kg, or neostigmine, 0.05 mg/kg, in a mixture with atropine or glycopyrrolate. The subsequent recovery of neuromuscular transmission was recorded for at least 10 min in all patients. Antagonism of block was considered adequate when a TOF ratio of 0.7 or more was attained (12). Further assessment of the patients was carried out in the recovery ward for at least 30 min using clinical criteria such as the ability to open eyes, cough, and show a sustained head lift. If adequate antagonism was not attained in 10 min, the patients received further doses of the anticholinesterase equivalent to half the initial dose.

The following measurements were made in both groups: $T_1$—height of the first twitch in the TOF (as a percentage of the control value before administration of any relaxant); TOF ratio—the ratio between the fourth and the first twitch in the same TOF sequence (these two parameters were measured before and after antagonism); time to onset of measurable effect of antagonism; time taken to attain a TOF ratio of 0.7; and TOF ratio at various degrees of recovery of $T_1$. The results in the two groups were compared using Student's *t*-test.

## Results

The groups were comparable with regard to average ages and weights (Table 1). The degree of neuromuscular block present in the two groups prior to administration of the antagonist was similar both in terms of $T_1$ as well as the TOF ratio (Table 1). Six patients in the edrophonium group and five in the neostigmine group did not show all four responses to TOF stimulation at the time of attempted reversal. The height of $T_1$ in these patients was 15 and 12%, respectively.

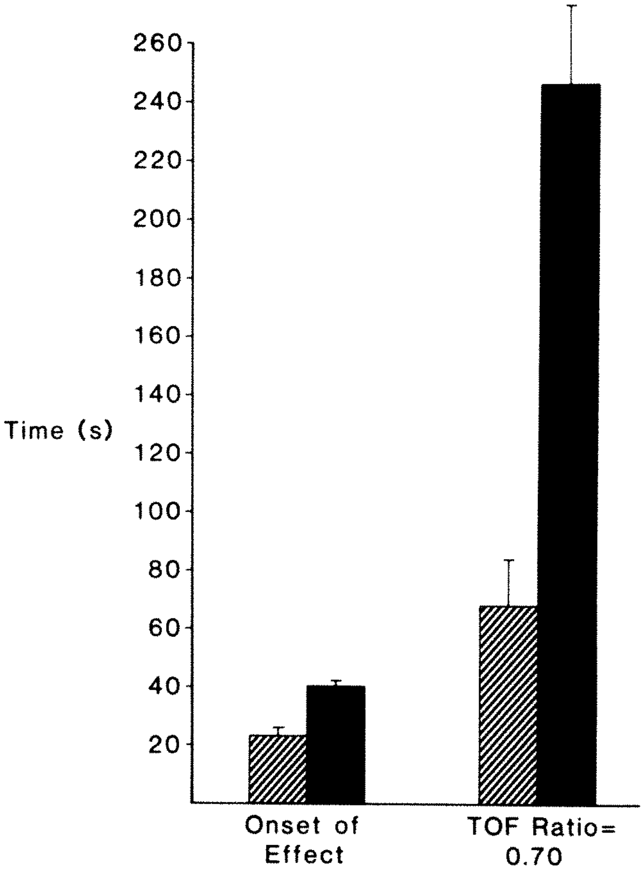


Figure 1. Mean time ± SEM to onset of effect and TOF ratio of 0.7 after edrophonium (stripes) and neostigmine (solid). Difference between edrophonium and neostigmine is significant ($P < 0.001$) for both parameters.

The time to onset of a measurable effect (Fig. 1) was 23 sec in those receiving edrophonium; this was significantly shorter ($P < 0.001$) than the 40 sec in those receiving neostigmine. Similarly, the time taken to attain a TOF ratio of 0.7 was significantly less ($P < 0.001$) in those receiving edrophonium, 68 sec; as compared to 246 sec in those given neostigmine. However, in the edrophonium group, this time relates to only 13 patients. The remaining seven patients failed to attain a TOF ratio of 0.7 with the initial dose of this anticholinesterase agent, as seen in Figure 2; which also shows the maximal TOF ratios attained in the individual patients and the average values for the two groups. The peak TOF ratios in individual patients varied from 0.71 to 1.0 with a mean of 0.87 ± 0.020 (SEM) in the neostigmine group. The corresponding values in the edrophonium group ranged from 0.40 to 1.0, with a significantly lower ($P < 0.05$) mean value of 0.77 ± 0.043 (SEM). However, if the seven patients in the edrophonium group who did not attain a TOF ratio of 0.70 are excluded, the average

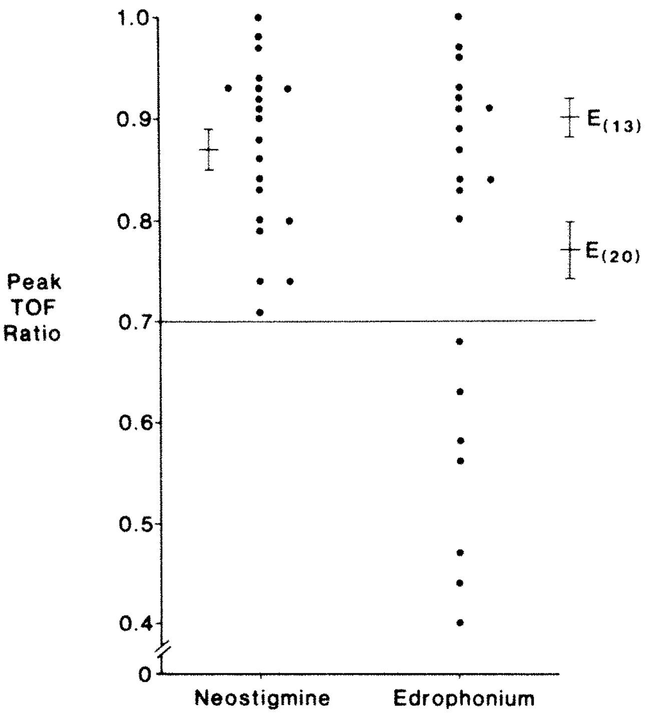


Figure 2. Peak TOF ratios in individual patients after administration of edrophonium and neostigmine. Horizontal line and the bars represent mean ± SEM values. $E_{(13)}$, average peak TOF ratio in the 13 patients in the edrophonium group who attained adequate antagonism (TOF of 0.7 or more). $E_{(20)}$, average peak TOF ratio in all 20 patients in the edrophonium group.

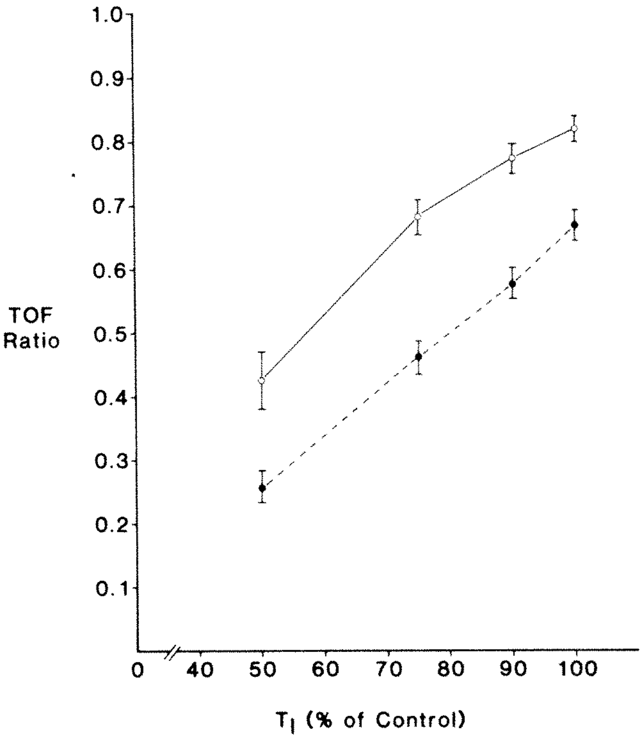


Figure 3. Relationship of TOF ratio and $T_1$ twitch height during antagonism of block after administration of edrophonium (open circles, $n = 13$) and neostigmine (closed circles, $n = 20$). The data shown is mean TOF ratio ± SEM at each point. Difference between edrophonium and neostigmine is significant ($P < 0.001$) at each point.

peak TOF was 0.90 ± 0.017 (SEM), a value not significantly different from the patients in the neostigmine group.

Five of the six patients who did not show all four responses to TOF stimulation prior to antagonism of residual block with edrophonium failed to reverse adequately. The sixth achieved a peak TOF ratio of 0.80. Two other patients also failed to achieve a TOF ratio of 0.70 after administration of edrophonium (7 out of 20); their TOF ratios prior to reversal were 0.07 and 0.18. These seven patients were all adequately reversed after administration of one additional dose of 0.25 mg/kg in five patients and two such doses in two patients. In contrast, all 20 patients whose residual block was antagonized with neostigmine achieved a peak TOF ratio greater than 0.70—including five patients who did not show all four responses to TOF stimulation prior to administration of neostigmine.

Figure 3 shows the TOF ratios at various degrees of recovery of $T_1$ for patients in the two groups whose blocks were adequately antagonized (TOF $\geq 0.70$). It is clear that the TOF ratios during antagonism are significantly higher ($P < 0.001$) after edrophonium at $T_1$ twitch heights ranging from 50–100% of control. However, those patients, who did not attain a TOF of 0.70 or more after reversal showed a greater degree of fade as evidenced by attaining an average TOF ratio of only 0.51 ± 0.049 (SEM), when $T_1$ had just reached control value.

## Discussion

Edrophonium, in a dose of 0.5 mg/kg or more, has been reported to produce a sustained antagonism of pancuronium and *d*-tubocurarine blocks (4–6). All these studies have shown edrophonium to have a more rapid onset of action and shorter time to peak effect compared to neostigmine. These findings are confirmed in the present study. Recently similar results have been reported during antagonism of atracurium-induced neuromuscular block (9,10).

In our study, 35% (7 out of 20) patients failed to be adequately reversed (TOF of 0.7) after edrophonium, 0.5 mg/kg; most of these did not show all four responses to TOF stimulation before antagonism. In contrast, all 20 patients receiving neostigmine were adequately reversed. Jones et al. (10) used edrophonium in the same dose as in the present study for antagonism of atracurium block, but did not give any information regarding failure, if any, to achieve adequate antagonism. In addition, they used a relatively small single dose of atracurium (0.25 mg/kg), and employed a TOF ratio of 0.5 to represent adequate antagonism in contrast to the commonly recommended TOF ratio of 0.7 used in our study. Similar findings of inadequate antagonism have been reported when edrophonium is used to antagonize relatively deep blocks produced not only by pancuronium (3) and alcuronium (13) but also by atracurium (14,15). Conflicting results regarding the efficacy of edrophonium may be due, in part, to the use of differing doses of the drug, ranging from 0.3 mg/kg (14) to 1 mg/kg (13). The ratio of 10:1 for the potency of neostigmine and edrophonium used in our study was based on the findings of Cronnelly et al. (5), who determined this ratio while antagonizing a steady-state *d*-tubocurarine block. However, in a situation more akin to routine anesthetic practice, Bevan et al. showed the potency ratios of neostigmine and edrophonium to be 16:1 (16).

It may be possible that a larger initial dose of edrophonium might have achieved adequate antagonism of block in all our patients. Indeed, this appears to have been so, because one or two additional doses of edrophonium attained adequate antagonism in those patients failing to reach a TOF ratio of 0.7 or more with the initial dose of 0.5 mg/kg. However, it is also possible that further spontaneous recovery of block was taking place in the intervening period of 10 min or more. This was suggested by Hughes et al. (17) who antagonized deeper atracurium-induced neuromuscular block.

The finding that edrophonium is associated with less fade than neogstigmine, as measured by TOF ratio, has been reported previously (10,18). In the present study, we found this to be the case at all points of recovery of $T_1$ up to, and including, the point at which $T_1$ attained 100% of its control value. In contrast, Donati et al. found the TOF ratio during antagonism with edrophonium to be greater than that after neostigmine only up to a $T_1$ of 70% of control (18). This phenomenon may reflect a marked presynaptic effect of this agent and was the reason given by Jones et al. (10) for the fact that edrophonium achieved superior antagonism of atracurium-induced block. Such presynaptic activity appears to be of benefit only in patients who attain adequate recovery, because patients failing to reach a TOF ratio of 0.7 showed a greater degree of fade in a TOF sequence.

In conclusion, edrophonium effectively antagonizes atracurium-induced block, provided all four responses to TOF stimulation are present. In patients with three or fewer responses to TOF stimulation, antagonism is incomplete with edrophonium, and a more reliable reversal of neuromuscular block is obtained with neostigmine.

The authors are grateful to Professor RSJ Clarke for his valuable comments and to Miss Sharon Connery for typing the manuscript.

## References

1. Hunter AR. Tensilon: a new anti-curare agent. Br J Anaesth 1952;24:175–86.
2. Katz RL. Neuromuscular effects of *d*-tubocurarine, edrophonium and neostigmine in man. Anesthesiology 1967;28:327–36.
3. Kopman AF. Edrophonium antagonism of pancuronium-induced neuromuscular blockade in man. Anesthesiology 1979;51:139–42.
4. Bevan DR. Reversal of pancuronium by edrophonium. Anaesthesia 1979;34:614–9.
5. Cronnelly R, Morris RB, Miller RD. Edrophonium: duration of action and atropine requirement in humans during halothane anesthesia. Anesthesiology 1982;57:261–6.
6. Morris RB, Cronnelly R, Miller RD, Stanski DR, Fahey MR. Pharmacokinetics of edrophonium and neostigmine when antagonizing *d*-tubocurarine neuromuscular block in man. Anesthesiology 1981;54:399–402.
7. Ferguson A, Egerszegi P, Bevan DR. Neostigmine, pyridostigmine and edrophonium as antagonists of pancuronium. Anesthesiology 1980;53:390–4.
8. Mirakhur RK. Antagonism of the muscarinic effects of edrophonium with atropine or glycopyrrolate: a comparative study. Br J Anaesth 1985;57:(in press).
9. Baird WLM, Kerr WJ. Reversal of atracurium with edrophonium. Br J Anaesth 1983;55:63S-65S.
10. Jones RM, Pearce AC, Williams JP. Recovery characteristics following antagonism of atracurium with neostigmine or edrophonium. Br J Anaesth 1984;56:453–7.
11. Viby-Mogensen J. Clinical evaluation of neuromuscular transmission. Br J Anaesth 1982;54:209–23.
12. Ali HH, Saverese JJ, Lebowitz PW, Ramsey FM. Twitch, tetanus and train-of-four as indices of recovery from nondepolarizing neuromuscular blockade. Anesthesiology 1981;54:294–7.
13. Harper NJN, Bradshaw EG, Healy TEJ. Antagonism of alcuronium with edrophonium or neostigmine. Br J Anaesth 1984;56:1089–94.
14. Yang E, Lee C, Tran B. Optimum dose of edrophonium for reversal of atracurium neuromuscular block. Anesth Analg 1984;63:283.
15. Rupp SM, McChristian JW, Miller RD. Neostigmine antagonizes a profound neuromuscular block more rapidly than edrophonium. Anesthesiology 1984;A297.
16. Bevan DR, Doherty WG, Breen PJ, Donati F. Mixtures of neostigmine and edrophonium are not synergistic. Anesthesiology 1984;A298.
17. Hughes R, Astley BA, Payne JP. Reversal of atracurium blockade by neostigmine and edrophonium. Br J Anaesth 1984;56:796P.
18. Donati F, Ferguson A, Bevan DR. Twitch height and train-of-four ratio after antagonism of pancuronium with edrophonium, neostigmine or pyridostigmine. Anesth Analg 1983;62:314–6.

ANESTH ANALG 871
1985;64:871–6

# Etomidate versus Thiopental for Induction of Anesthesia

Jeffrey L. Giese, MD, Randall J. Stockham, MD, Theodore H. Stanley, MD,
Nathan L. Pace, MD, and Rob H. Nelissen, DrS

GIESE JL, STOCKHAM RJ, STANLEY TH, PACE NL, NELISSEN RH. Etomidate versus thiopental for induction of anesthesia. Anesth Analg 1985;64:871–6.

*Hemodynamic changes and side effects of anesthesia induction with etomidate or thiopental were evaluated in 83 ASA class I or II patients. Patients were randomly assigned to one of 12 groups according to pretreatment drug (fentanyl, 100 μg, or normal saline intravenously), induction agent (etomidate, 0.4 mg/kg, or thiopental, 4 mg/kg), and maintenance anesthetic technique (isoflurane–oxygen, isoflurane–nitrous oxide–oxygen, or fentanyl–nitrous oxide–oxygen). The purpose of this experiment, of factorial design, was to evaluate the combined effects of two or more experimental variables used simultaneously and to observe interaction effects. There were significant increases in heart rate in all groups, especially after tracheal intubation. These increases were attenuated but not eliminated by fentanyl pretreatment. Systolic arterial blood pressure increased significantly after intubation and was not affected either by fentanyl pretreatment or by the induction agent. Patients in whom anesthesia was induced with etomidate had a greater incidence of pain on injection and myoclonus and a lesser incidence of apnea than patients in whom anesthesia was induced with thiopental. Fentanyl pretreatment significantly decreased the incidence of pain on injection and myoclonus, but it increased the incidence of apnea when anesthesia was induced with etomidate. The incidence of postoperative nausea and vomiting was similar after thiopental and etomidate and was unaffected by fentanyl pretreatment. However, patients in whom anesthesia was maintained with isoflurane (with and without nitrous oxide) had a significantly lower incidence of nausea and vomiting than did patients given fentanyl–$N_2O$–$O_2$ for maintenance of anesthesia. These results indicate that there is no significant difference between etomidate and thiopental as anesthetic induction agents in healthy patients. Pretreatment with a small dose of fentanyl attenuates the increases in heart rate associated with induction of anesthesia and tracheal intubation with either etomidate or thiopental, and reduces but does not eliminate side effects associated with etomidate induction.*

Key Words: INDUCTION, ANESTHESIA—etomidate, thiopental. ANESTHETICS, INTRAVENOUS—etomidate, thiopental.

Etomidate is a rapid-acting, γ-aminobutyric acid (GABA) receptor-stimulating, sedative/hypnotic agent with little or no cardiovascular or respiratory effects (1–8). Because of these properties, and its high therapeutic index (six times that of thiopental), etomidate may be particularly useful as an anesthetic induction agent in patients with poor cardiovascular reserve (2–4). Unfortunately, etomidate has no analgesic properties and produces several annoying side effects, including pain on injection, myoclonus, and postoperative nausea and vomiting (9). Tracheal intubation after anesthetic induction with etomidate can result in significant increases in heart rate and arterial blood pressure. These changes have been attributed to absence of analgesia, and are similar to increases in heart rate and arterial pressure found when intubation follows anesthetic induction with thiopental, midazolam, and other sedative/hypnotic agents without analgesic properties (10).

Some investigators have found that intravenous administration of a small dose of a narcotic analgesic prior to injection of etomidate and use of a larger (forearm) vein can reduce the incidence of pain on injection and myoclonus without altering the cardiovascular and respiratory properties of the drug (11). This therapy might also reduce or eliminate increases in heart rate and arterial blood pressure that accompany tracheal intubation, but this has not been carefully studied. Other investigators have suggested, but not carefully documented, that avoidance of nitrous

---

This study was supported in part by grants from Abbott Laboratories, Stanley Research Foundation, and NIH Anesthesia Training Grant #GM07613-05.

Received from the Department of Anesthesiology, University of Utah School of Medicine, Salt Lake City, Utah. Accepted for publication March 26, 1985.

Address correspondence to Dr. Stanley, Professor of Anesthesiology, Department of Anesthesiology, University of Utah Medical Center, 50 North Medical Drive, Salt Lake City, UT 84132.

© 1985 by the International Anesthesia Research Society

oxide (P. Janssen, personal communication) or inclusion of a potent inhalation agent (B. Cohen, personal communication) for maintenance of anesthesia reduces the incidence of postoperative nausea and vomiting after anesthetic induction with etomidate.

We are unaware of any study that compared induction of anesthesia with etomidate and thiopental and includes consideration of pretreatment medications, the maintenance anesthetic agents (including the presence or absence of $N_2O$), and the possible combined effects or interactions of two or more of the experimental variables outlined above. Thus this study was designed to evaluate and compare the changes in arterial blood pressure, heart rate, and the side effects associated with anesthetic induction with etomidate and thiopental. Simultaneously, factors (both combined and separate, i.e., opioid pretreatment, different anesthetic maintenance regimens, size of vein used for injection) that might ameliorate changes in blood pressure and heart rate, and decrease the incidence of induction and postoperative side effects were also studied.

## Methods

The study was approved by the University of Utah Health & Sciences Center Institutional Review Board. Eighty-three ASA class I or II patients, 18–75 yr, undergoing elective general, gynecological, or orthopedic surgical procedures served as the experimental subjects. All patients gave their written informed consent for participation in the study.

After enrollment in the study, patients were randomly allocated to one of 12 groups. Randomization was not restricted to force groups of equal size. The study continued until every group had at least six patients. The groups varied according to their preanesthetic induction treatment, induction agent, and technique used for maintenance of anesthesia (Table 1). The study design was a 2 × 2 × 2 × 2 factorial experiment with repeated measures. The factorial design was incomplete in that only 12 rather than 16 groups were used; no patient received fentanyl alone for maintenance of anesthesia. The investigators recording hemodynamics and side effects were aware of the induction and maintenance agents but not the pretreatment drug.

All patients were premedicated with atropine sulfate (0.4 mg intramuscularly) and diazepam (0.1 mg/kg orally) 1 hr prior to the scheduled time of operation. Upon arrival in the operating room, an intravenous infusion was started in either a forearm or hand vein, an automatic blood pressure cuff was applied to an upper arm, and a bipolar lead II electrocardiogram displayed continuously. After a 5-min stabilization period, the pretreatment drug (fentanyl, 100 μg; or saline, 2 ml) was administered intravenously, and the patients were preoxgenated with 100% oxygen via a face mask. Three min after pretreatment, etomidate (0.4 mg/kg) or thiopental (4 mg/kg) was given as a bolus intravenous injection over 15–30 sec. Two min after administration of the induction agent, all patients were paralyzed with succinylcholine (1.0 mg/kg intravenously), and their tracheas were intubated under direct vision.

Table 1. Assignment of 83 Patients to 12 Groups Varying in Pretreatment, Anesthetic Induction Agent, and Maintenance Anesthetic Technique

| Number of patients | Induction agent | Pretreatment | Maintenance technique |
|---|---|---|---|
| 6 | Etomidate | Fentanyl | Isoflurane–$O_2$ |
| 6 | Etomidate | Fentanyl | Isoflurane–$N_2O$–$O_2$ |
| 8 | Etomidate | Saline | Isoflurane–$N_2O$–$O_2$ |
| 6 | Etomidate | Saline | Isoflurane–$O_2$ |
| 9 | Etomidate | Fentanyl | Fentanyl–$N_2O$–$O_2$ |
| 10 | Etomidate | Saline | Fentanyl–$N_2O$–$O_2$ |
| 6 | Thiopental | Fentanyl | Isoflurane–$O_2$ |
| 7 | Thiopental | Saline | Isoflurane–$O_2$ |
| 6 | Thiopental | Fentanyl | Isoflurane–$N_2O$–$O_2$ |
| 7 | Thiopental | Saline | Isoflurane–$N_2O$–$O_2$ |
| 6 | Thiopental | Fentanyl | Fentanyl–$N_2O$–$O_2$ |
| 6 | Thiopental | Saline | Fentanyl–$N_2O$–$O_2$ |

During the induction sequence, the presence or absence of myoclonus (nonspecific muscle contractions unassociated with succinylcholine administration) and pain on injection (volunteered by the patient or solicited by the investigator if the patient grimaced) were noted. Systolic, diastolic, and mean arterial blood pressures, and heart rate were measured on arrival in the operating room (baseline), 3 min after injection of the pretreatment agent, 2 min after administration of the induction agent, 1 min after succinylcholine administration, and 1 min after tracheal intubation.

After anesthetic induction and tracheal intubation, anesthesia was initially maintained with either isoflurane (0.5–3%, inspired concentration) plus nitrous oxide (50%) in oxygen, isoflurane (1–4%) in oxygen, or fentanyl (10 μg/kg bolus, intravenously) plus $N_2O$ (50%) in oxygen. Systolic arterial blood pressure was maintained within 15% of baseline levels by adjusting the inspired concentration of isoflurane, or by administration of incremental boluses (50–100 μg) of intravenous fentanyl. All patients were paralyzed with pancuronium (1–4 mg, intravenously) 10–15 min after anesthetic induction when train-of-four twitch monitoring of the facial muscles indicated dissipation of succinylcholine-induced neuromuscular blockade. Paralysis was maintained with additional increments

Table 2. Age, Gender, and Operative Times

| | Pretreatment | | Induction agent | | Maintenance agent | | $N_2O$ | |
|---|---|---|---|---|---|---|---|---|
| | Saline | Fentanyl | Thiopental | Etomidate | Fentanyl | Isoflurane | Yes | No |
| Number of patients | 44 | 39 | 38 | 45 | 31 | 52 | 58 | 25 |
| Age | 35 ± 1.9 | 39 ± 2.5 | 36 ± 2.3 | 37 ± 2.1 | 37 ± 2.5 | 37 ± 2.0 | 37 ± 1.9 | 35 ± 2.8 |
| Anesthesia duration (min) | 144 ± 10.1 | 135 ± 10.9 | 133 ± 10.8 | 146 ± 10.1 | 140 ± 10.9 | 140 ± 9.9 | 138 ± 8.3 | 143 ± 15.2 |
| Surgery duration (min) | 102 ± 9.0 | 90 ± 10.8 | 92 ± 10.0 | 101 ± 9.7 | 95 ± 10.1 | 98 ± 9.4 | 98 ± 7.9 | 94 ± 14.3 |
| Gender (male/female) | 14/30 | 11/28 | 12/26 | 13/32 | 10/21 | 15/37 | 18/40 | 7/18 |

Values shown are mean ± SEM and frequency counts.

of pancuronium (1–2 mg, intravenously) as needed (via twitch–tetanus or train-of-four evaluation) every 45–60 min. At the conclusion of the operation, residual neuromuscular blockade was reversed with neostigmine (3–5 mg, intravenously) and glycopyrrolate (0.4–0.8 mg, intravenously), and the patients were extubated when ventilation was deemed adequate (i.e., ventilatory rate ≥ 10 breaths/min and estimated tidal volume ≥ 350 ml). Patients were then transported to the recovery room.

The patients were observed continuously in the recovery room, and were interviewed 24–48 hr postoperatively to determine the degree of pain at the site of the intravenous infusion and the presence or absence of postoperative nausea and vomiting. In addition, the intravenous infusion site was inspected for evidence of phlebitis (redness, tenderness).

Statistical analysis of the data employed a factorial design with repeated measures. The purpose of a factorial experiment is to evaluate the combined effects of two or more experimental variables when used simultaneously (12). Thus instead of comparing the hemodynamics and side effects of the twelve groups, comparisons were made between the levels of the factors (i.e., saline vs fentanyl, thiopental vs etomidate). Factorial experiments also allow the evaluation of interaction effects. An interaction effect is an effect attributable to the combination of variables above and beyond that which can be predicted from the variables considered singly (12).

Age, anesthesia time, duration of surgery, baseline heart rate, and baseline systolic blood pressure were analyzed for statistical significance by analysis of variance (ANOVA). Comparisons of heart rate and of systolic blood pressure during the induction period (3 min after pretreatment to 1 min after intubation) were analyzed for statistical significance via multivariate analysis of covariance (MANCOVA) and multivariate analysis of covariance for repeated measures (repeated measures MANCOVA); baseline heart rate or systolic blood pressure was the covariate. If joint statistical hypotheses were statistically significant, individual comparisons were performed by univariate ANOVAs. MANCOVA requires complete cases (data for each variable in every patient); patients were deleted from analysis if complete data were not available. To simplify data presentation, only systolic blood pressure is presented. Analysis of mean and diastolic blood pressure is available on request. Frequency counts were analyzed for statistical significance using $\chi^2$-tests and stepwise logistic regression analysis. Statistical software was from the BMDP statistical library, in particular the P1D, P4F, PLR, and P4V programs. $P < 0.05$ was considered statistically significant.

## Results

Twenty-five male and fifty-eight female patients served as experimental subjects. There were no differences in age, male or female ratio, time of anesthesia, or duration of surgery for the four study factors (Table 2). During the induction period (3 min after pretreatment to 1 min after intubation) heart rate after saline pretreatment was higher than after fentanyl pretreatment (MANCOVA: $F(4,75) = 4.28$; $P = 0.0036$); specifically, heart rate was higher 2 min after induction, 1 min after succinylcholine, and 1 min after intubation (Table 3). There was no difference in heart rate between the two induction agents, thiopental and etomidate, during the induction period. Compared with heart rate 3 min after pretreatment, heart rate increased during the induction period (repeated measures MANCOVA; $F(3,237) = 60.45$; $P = 0.0000$). Increases in heart rate during the induction period were similar in patients receiving etomidate and thiopental; increases in heart rate were significantly less in those pretreated with fentanyl compared to saline, irrespective of induction agent (repeated measures MANCOVA; $F(3,237) = 2.86$; $P = 2.86$; $P = 0.0377$). There was no interaction between pretreatment and induction agent on heart rate.

Only 79 patients had complete data for analysis of

Table 3. Heart Rate during Induction (beats/min)

| | Baseline | 3 min after pretreatment | 2 min after induction | 1 min after succinylcholine | 1 min after intubation |
|---|---|---|---|---|---|
| Preatment | | | | | |
| Saline ($n$ = 44) | 78 ± 2.3 | 79 ± 2.2 | 86 ± 2.2 | 99 ± 2.7 | 105 ± 3.2 |
| Fentanyl ($n$ = 39) | 83 ± 2.1 | 81 ± 2.5 | 78 ± 1.7$^{a}$ | 90 ± 2.5$^{a,b}$ | 100 ± 3.0$^{a,c}$ |
| Induction agent | | | | | |
| Thiopental ($n$ = 38) | 79 ± 2.3 | 78 ± 2.4 | 83 ± 2.0 | 95 ± 2.8 | 105 ± 3.0 |
| Etomidate ($n$ = 45) | 82 ± 2.2 | 81 ± 2.2 | 81 ± 2.2 | 95 ± 2.8$^{b}$ | 101 ± 3.0$^{c}$ |

Values shown are mean ± SEM.
[a] $P < 0.05$ saline vs fentanyl.
[b] $P < 0.05$ 1 min after succinylcholine vs 3 min after pretreatment.
[c] $P < 0.05$ 1 min after intubation vs 3 min after pretreatment.

systolic blood pressure (Table 4). By chance, patients who were to receive fentanyl had a higher baseline systolic blood pressure (ANOVA; F(1,79) = 10.7; $P = 0.0016$). All comparisons were thus adjusted by use of baseline systolic blood pressure as a covariate. There was no difference in systolic blood pressure between saline and fentanyl, or between thiopental and etomidate during the induction period. Compared with systolic blood pressure 3 min after pretreatment, all patients analyzed as a single group experienced an initial decrease in pressure at 2 min after induction, followed by increases in pressure at 1 min after succinylcholine and 1 min after intubation (repeated measures MANCOVA; F(3,225) = 70.69; $P = 0.0000$). Systolic blood pressure did not decrease with saline pretreatment 2 min after induction (repeated measures MANCOVA; F(1,75) = 7.55; $P = 0.0075$). There was no interaction between pretreatment and induction agent on systolic blood pressure. Fentanyl pretreatment did not affect the increase in systolic blood pressure during the induction period.

Induction of anesthesia with etomidate was associated with a greater incidence of pain on injection and myoclonus but a lower incidence of apnea than induction with thiopental (Table 5). Pretreatment with fentanyl significantly reduced the incidence of pain on injection and myoclonus, but increased the incidence of apnea compared to saline pretreatment (Table 5). There was no interaction between pretreatment group and induction drug on the incidence of apnea, myoclonus, and pain on injection. The incidence of myoclonus during anesthetic induction with etomidate was significantly greater in females (31%) than in males (20%) ($\chi^2 = 10.6$, $P = 0.001$). There was no interaction among the induction drug, pretreatment group, and gender on the incidence of myoclonus. Pain on injection was significantly more frequent when etomidate was injected into a dorsal hand vein (83%) than when injected into a forearm vein (44%) ($\chi^2 = 4.08$, $P = 0.043$), but was significantly and equally reduced by pretreatment with fentanyl (46% in a hand vein vs 12% in forearm vein; $\chi^2 = 5.4$; $P = 0.02$).

Although females were significantly more likely to experience nausea and vomiting than were males (67% vs 21%) ($\chi^2 = 15.3$; $P < 0.0001$), neither the induction agent nor the presence of nitrous oxide in the maintenance technique significantly affected the incidence of postoperative nausea or vomiting. In contrast, patients administered anesthesia maintained with fentanyl suffered from postoperative nausea and vomiting significantly more frequently (73%) than those receiving isoflurane (42%; $\chi^2 = 10.0$; $P = 0.002$).

The overall incidence of intravenous site phlebitis was 18%. The incidence of phlebitis was not related to the induction agent, site of intravenous infusion, pretreatment drug, or maintenance technique.

## Discussion

The results of this study demonstrate that etomidate, when used as an anesthetic induction agent without analgesic supplementation, provides no advantages over thiopental in healthy ASA class I or II patients. Indeed, the higher incidence of annoying side effects (pain on injection and myoclonus) are probably greater negative features of the compound than its one possible advantage (less apnea) in these healthy patients). A recent report demonstrating inhibition of adrenal steroidogenesis after anesthetic induction is another factor that needs to be studied (13). Our data show that the side effects of etomidate can be significantly decreased, but not totally eliminated, by selection of an appropriate vein and use of a small (100 μg) preinduction dose of fentanyl. This same dose of fentanyl is also effective in blunting, but not preventing, increases in heart rate that accompany tracheal intubation whether anesthesia is induced with etomidate or thiopental. The small dose of fentanyl used in this study did not effectively blunt increases in arterial blood pressure that accompanied tracheal

Table 4. Systolic Arterial Pressure during Induction (mm Hg)

| | Baseline | 3 min after pretreatment | 2 min after induction | 1 min after succinylcholine | 1 min after intubation |
|---|---|---|---|---|---|
| Pretreatment | | | | | |
| Saline ($n$ = 40) | 117 ± 3.0 | 115 ± 3.1 | 116 ± 3.9 | 126 ± 3.8 | 145 ± 4.3 |
| Fentanyl ($n$ = 39) | 131 ± 3.1[a] | 126 ± 2.9 | 117 ± 2.7[d] | 128 ± 4.2[b] | 149 ± 4.3[c] |
| Induction agent | | | | | |
| Thiopental ($n$ = 38) | 121 ± 2.9 | 119 ± 2.8 | 114 ± 2.9 | 127 ± 3.7 | 147 ± 4.2 |
| Etomidate ($n$ = 41) | 126 ± 3.5 | 122 ± 3.3 | 119 ± 3.7[d] | 126 ± 4.2[b] | 147 ± 4.4[c] |

Values shown are mean ± SEM.

[a] $P < 0.05$ saline vs fentanyl.

[b] $P < 0.05$ 1 min after succinylcholine vs 3 min after treatment.

[c] $P < 0.05$ 1 min after intubation vs 3 min after pretreatment.

[d] $P < 0.05$ 2 min after induction vs 3 min after pretreatment.

intubation after induction with etomidate or thiopental. Finally, we could find no evidence of an increased incidence of nausea and vomiting after anesthetic induction with etomidate, as compared to thiopental. Nor did we find that the subsequent use of nitrous oxide caused an increased incidence of postoperative nausea and vomiting. However, the use of a nitrous oxide–oxygen plus a narcotic (fentanyl) anesthetic technique led to an increased incidence of nausea and vomiting when compared to isoflurane–$O_2$ or isoflurane–$N_2O$–$O_2$.

This study did not evaluate the proposed advantages of anesthetic induction with etomidate in patients with limited cardiovascular reserve and therefore may not be directly applicable to that group. Nonetheless, our results raise the question of whether etomidate or any other compound without analgesic properties should be promoted as an "anesthetic induction" agent in patients who are at potential risk from increases in myocardial oxygen consumption secondary to increases in heart rate and arterial blood pressures associated with anesthetic induction, tracheal intubation, or both. That a compound like etomidate does not impair cardiovascular dynamics and myocardial mechanics (not measured in this study) during the induction sequence is of obvious benefit. However, it is also of great importance that an induction agent has the ability to blunt or eliminate changes in hemodynamics that may impair myocardial oxygen supply/demand ratios during the stressful period of tracheal intubation. Although the appropriate use of fentanyl, another opioid, or any other compound that blunts cardiovascular responses during induction and intubation, may make etomidate a better anesthetic induction agent, the fentanyl dose used in this study was only minimally effective. Furthermore, it appears from our data that fentanyl provides the same hemodynamic advantages for thiopental. The question, then, is not only whether etomidate or thiopental or any other sedative/hypnotic anesthetic induction agent is less depressant to the myocardium in patients with limited cardiovascular reserve, but rather which mixture of agents (sedative/hypnotic, opioid, local anesthetic, volatile agent) and range of doses of these agent(s) provide the most ideal conditions throughout the induction–intubation sequence. An additional question is whether the agent or mixture of agents results in other effects that are beneficial or detrimental.

Although we found no "interaction effects" in this study (interactions above and beyond those we expected from the drug effects considered separately), fentanyl pretreatment (100 μg, intravenously) resulted in decreased incidences of pain on injection, myoclonus, and no effect on postoperative nausea and vomiting, but an increased incidence of apnea. Maintenance of anesthesia with fentanyl plus $N_2O$ increased the incidence of postoperative nausea and vomiting. These properties of fentanyl and other opioids used as analgesic supplements during anesthesia have been reported before (3–5,11,14); however, our methodological and statistical approach allowed us to confirm that postoperative nausea and vomiting was due to fentanyl given during operation, not due to the nitrous oxide component of the nitrous oxide–narcotic maintenance anesthetic or the pretreatment or induction agent. The latter result is particularly important because it suggests that fentanyl supplementation during operation (which is usually a component of anesthetic techniques that employ etomidate (3,4,14,15)), may be a more important culprit in the postoperative nausea and vomiting usually attributed to etomidate.

One could speculate that if blockade of hemodynamic responses to anesthetic induction and tracheal intubation, and prevention of pain on injection and myoclonus are important, a higher pretreatment dose of fentanyl before etomidate may be more effective. Indeed, a recent study from our institution has demonstrated that 3–4 μg/kg of fentanyl before etomidate

Table 5. Incidence of Side Effects with Anesthetic Induction

| | Apnea | Myoclonus | Pain on injection |
|---|---|---|---|
| Induction agent | | | |
| Thiopental ($n$ = 38) | 87(33) | 0(0) | 5(2) |
| Etomidate ($n$ = 45) | 49(22)[a] | 51(23)[a] | 44(20)[a] |
| Pretreatment group | | | |
| Saline ($n$ = 44) | 45(20) | 45(20) | 34(15) |
| Fentanyl ($n$ = 39) | 90(35)[b] | 8(3)[b] | 18(7)[c] |

Values shown are % (number of patients).

[a] $P < 0.00005$ thiopental vs etomidate.

[b] $P < 0.00005$ saline vs fentanyl.

[c] $P < 0.02$ saline vs fentanyl.

totally eliminated all increases in heart rate and arterial blood pressure produced by the induction–intubation sequence (without resulting in hypotension and a reduction in cardiac output), and further reduced the incidence of pain on injection (15). Even more recent data (Stockham R, Stanley TH, Pace NL, unpublished results) indicate that total elimination of pain on injection and myoclonus during induction with etomidate can be achieved but requires much higher pretreatment doses of fentanyl, 7 μg/kg.

The mechanism for etomidate-induced myoclonus is not known but has been thought to be associated with disinhibition of subcortical structures (16). The mechanism by which fentanyl decreases myoclonus associated with etomidate is also not known. However, there are data that suggest that fentanyl stimulates opioid μ-receptors on GABA-nergic neurons in the basal ganglia (17). Activation of these receptors may decrease or modify release of GABA from GABA-nergic neurons, or even modify GABA-receptor function. Pain on injection after etomidate has been attributed to the vehicle in which etomidate is dissolved, propylene glycol. The pain is greater after the use of an aqueous solution as compared to 35% propylene glycol solution (14). The mechanism responsible for the decrease in pain on injection after pretreatment with fentanyl is unknown, but it is probably related to analgesia provided by the opioid.

In conclusion, our results indicate that there is no difference between etomidate and sodium thiopental as an anesthetic induction agent in healthy patients. Pretreatment with a small dose (100 μg) of fentanyl attenuated increases in heart rate associated with induction of anesthesia and tracheal intubation with either etomidate or sodium thiopental. Fentanyl pretreatment also reduced, but did not eliminate, side effects associated with etomidate. Postoperative nausea and vomiting, usually attributed to induction of anesthesia with etomidate, was found to be more closely associated with fentanyl used during anesthesia maintenance.

## References

1. Criado A, Maseda J, Navarro E, Escarpa A, Avello F. Induction of anaesthesia with etomidate: haemodynamic study of 36 patients. Br J Anaesth 1980;52:803–5.
2. Gooding JM, Weng JT, Smith RA, Berninger G, Kirby R. Cardiovascular and pulmonary responses following etomidate induction of anesthesia in patients with demonstrated cardiac disease. Anesth Analg 1979;58:40–1.
3. Tarnow J, Hess W, Klein W. Etomidate, althesin and thiopentone as induction agents for coronary artery surgery. Can Anaesth Soc J 1980;27:338–44.
4. Karliczek GF, Brenken V, Schokkenbroek R, VanderBrocke J, Richardson F, VanderHeide J. Etomidate–analgesic combinations for induction of anaesthesia in cardiac patients. Anaesthesist 1982;31:51–60.
5. Daehlin L, Gran L. Etomidate and thiopentone: a comparative study of their respiratory effects. Curr Ther Res 1980;27:706–13.
6. Doenicke A. Etomidate, a new intravenous hypnotic. Acta Anaesthesiol Belg 1975;25:5–8.
7. Reneman RS, Janssen PAJ. The experimental pharmacology of etomidate, a new potent, short acting intravenous hypnotic. In: Doenecke A, ed. Etomidate. Berlin:Springer Verlag, 1977:1–5.
8. Janssen PAJ, Niemegeers JE, Marsboom RPH. Etomidate, a potent nonbarbituate hypnotic: intravenous etomidate in mice, rats, guinea pigs, rabbits and dogs. Arch Int Pharmacodyn Ther 1975;214:92–132.
9. Shuemans V, Dom J, Pony J, Schujgrond H, Brugmans J. Multinational evaluation of etomidate for anesthesia induction. Anaesthesist 1978;27:52–9.
10. Nauta J, Stanley TH, de Lange S, Koopman D, Spierdyk J, Van Kleif J. Anaesthetic induction with alfentanil: comparison with thiopental, midazolam and etomidate. Can Anaesth Soc J 1983;30:53–60.
11. Holdcroft A, Morgan M, Whitwarm JG, Lumley J. Effect of dose and premedication on induction complications with etomidate. Br J Anaesth 1976;48:199–205.
12. Winer BJ. Statistical principals in experimental design. 2nd ed. New York:McGraw-Hill, 1971;309:430.
13. Wagner R, White P, Kan P, Rosenthal M, Feldman D. Inhibition of adrenal steroidogenesis by the anesthetic etomidate. N Engl J Med 1983;310:1415–21.
14. Giese J, Stanley T. Etomidate: a new intravenous anesthetic induction agent. Pharmacotherapy 1983;3:251–8.
15. Stockham RJ, Stanley TH, Groen F, Gillmor ST, Pace NL, King K. Fentanyl vs etomidate plus fentanyl for anesthetic induction in high risk patients. Anesth Analg 1985;64:290.
16. Krugler J, Doenicke A, Laub M. The EEG after etomidate. In: Doenecke A, ed. Etomidate. Berlin:Springer Verlag, 1977:31–48.
17. Havemann V, Kuschinsky K. Neurochemical aspects of the opioid-induced "catatonia." Neurochemistry International 1982;4:199–215.

ANESTH ANALG
1985;64:877–887

# A Comparison of Fentanyl–$O_2$ and Sufentanil–$O_2$ for Cardiac Anesthesia

Michael B. Howie, MD, Thomas D. McSweeney, BS, Rao P. Lingam, MD, and Stuart P. Maschke, MD

HOWIE MB, McSWEENEY TD, LINGAM RP, MASCHKE SP. A comparison of fentanyl–$O_2$ and sufentanil–$O_2$ for cardiac anesthesia. Anesth Analg 1985;64:877–887.

*In a prospective randomized study of 48 patients scheduled to undergo elective coronary artery surgery, sufentanil (20 μg/kg) was compared with fentanyl (100 μg/kg) anesthesia by assessing hemodynamic and plasma catecholamine level responses to surgery. At 15 points during the study, cardiovascular dynamics were recorded. At six points in the study, arterial blood was obtained for simultaneous assays of plasma concentrations of epinephrine, norepinephrine, and dopamine. Neither mean cardiovascular dynamics nor catecholamine concentrations were statistically significantly different between the groups preoperatively. Both agents provided generally stable hemodynamics during surgery. Sufentanil was associated with decreased systemic vascular resistance at several time points with concurrent increased cardiac index and heart rate. Although catecholamine levels increased somewhat during cardiopulmonary bypass in both groups, there were no signficiant differences between the groups at any point except that at chest closure patients given sufentanil had significantly lower dopamine concentrations than those given fentanyl. Times for recovery from surgery failed to show any difference between the two groups of patients. Blood pressure increases with patients given sufentanil compared favorably with those given fentanyl. We conclude that at these doses, with this surgery, there were no major clinical differences, though sufentanil produced significantly lower systemic vascular resistance at several events and had a lower plasma dopamine concentration after cardiopulmonary bypass.*

Key Words: ANESTHESIA, CARDIOVASCULAR. ANESTHETICS, INTRAVENOUS—sufentanil, fentanyl.

It has been suggested that the more potent an opiate analgesic, the more specific its action and the lower the incidence of side effects (1). Therefore sufentanil (S), a synthetic opiate analgesic 5–10 times as potent as fentanyl (F) in animals (1–4), may have advantages over F as a sole anesthetic agent for cardiac surgery. Initial reports have commented favorably on the use of S as a sole anesthetic agent (5–8). Protection against stress reactions in dogs was reported by de Castro (9) to be more complete with S than F. In other studies, S suppressed metabolic and endocrine responses to anesthesia and surgery but failed to prevent marked increases in plasma levels of hormones associated with cardiopulmonary bypass (CPB) and the early postoperative period (10,11).

Khoury et al. (6) gave S (7–10 μm/kg) by bolus injection for induction of anesthesia and found that 88% (15/17) of the patients required sodium nitroprusside to control blood pressure. When an F dose of 50 μg/kg was compared to an S dose of 10 μg/kg by Rosow et al. (12), they found that, in order to control hypertension, the percentage of patients given F (40%, 2/5) requiring supplemental vasodilators or potent inhalational agents was twice that of patients given S (20%, 1/5). Griesemer et al. (5) compared bolus induction doses of S (15 and 30 μg/kg) and reported hypertensive responses during sternotomy in 67% (4/6) and 17% (1/6) of the patients, respectively. Sebel et al. (8) were able to reduce the percentage of patients with hypertension during sternotomy (40%, 16/40) by supplementing the bolus induction dose of S (15 μg/kg) with subsequent increments (250–500 μg) of S (total dose mean 19.4 μg/kg). De Lange et al. (13) gave S (300 μg/min) infusions (total dose mean 12.9 μg/kg) and reported 11% (2/18) of the patients had increases in systolic arterial pressure (SAP) greater than 20% of control during sternotomy. Bovill et al. (11) reported that with an incremental S dose schedule (1,2, 3, and

---

Supported in part by a research grant from Janssen Pharmaceutica Inc.

Received from the Department of Anesthesiology, Ohio State University Hospitals, Columbus, Ohio. Accepted for publication April 4, 1985.

Address correspondence to Dr. Howie, Department of Anesthesiology, Ohio State University Hospitals, 410 West 10th Avenue, Columbus, OH 43210.

© 1985 by the International Anesthesia Research Society

Table 1. Patient Demographics

| | Fentanyl | | Sufentanil | |
|---|---|---|---|---|
| | Male mean (SD) | Female mean (SD) | Male mean (SD) | Female mean (SD) |
| Age (yr) | 55.23 | 62.25* | 57.87 | 47.67* |
| | (7.79) | (6.48) | (8.64) | (5.51) |
| Weight (kg) | 85.54 | 70.13 | 86.26 | 72.00 |
| | (14.47) | (12.50) | (11.93) | (14.93) |
| Body surface area (m$^2$) | 2.04 | 1.72 | 2.04 | 1.77 |
| | (0.18) | (0.16) | (0.15) | (0.15) |
| Control cardiac index (L·min$^{-1}$·m$^{-2}$) | 2.82 | 2.87 | 2.59 | 2.72 |
| | (0.45) | (0.53) | (0.58) | (0.13) |
| Ejection fraction (%) | 47.50 | 62.17 | 57.07 | 50.00 |
| | (14.61) | (9.83) | (14.34) | (13.10) |
| Number of graphs | 3.00 | 2.75 | 2.64 | 3.00 |
| | (0.58) | (1.17) | (0.85) | (1.00) |
| Number of patients | 14 | 8 | 23 | 3 |

*When sex was not considered there was no significant difference between the drug groups.

5 μg/kg) 33% (2/6) of the coronary artery surgery patients had increases in SAP greater than 20% of control during sternotomy. In view of conflicting data in previous studies, we undertook a prospective randomized trial comparing the cardiovascular dynamic and catecholamine stress responses to cardiac surgery performed by a single surgeon when either S (10, 5, and 5 μg/kg) or F (50, 25, and 25 μg/kg) was used for anesthesia, based on doses found adequate by others (5,8,10,11,13).

## Materials and Methods

Written, informed consent to participate was obtained from each of 48 patients (22 receiving F, 26 receiving S) scheduled to undergo elective coronary artery surgery (Table 1). The protocol was approved by the Human Subjects Review Committee of the Ohio State University. Patients taking propranolol were given ¼ their daily dose at the time of premedication, which consisted of oral lorazepam (0.05 mg/kg). In the operating suite, a radial arterial catheter, a 7-French balloon-tipped thermodilution pulmonary arterial catheter (model 93A-131, Edwards Laboratories Inc., Santa Ana, CA), and two wide bore, peripheral venous catheters were placed percutaneously under local analgesia.

After preoxygenation, pancuronium bromide (0.1 mg/kg) was given through the side port of the pulmonary arterial catheter introducer over 2 min, simultaneously with infusion of F (50 μg/kg) or S (10 μg/kg). Ventilation was then controlled manually with tracheal intubation, after the intratracheal administration of 4 ml of 4% lidocaine spray. At a rate of 10 breaths per minute, ventilation was continued with 100% oxygen at a tidal volume of 10 ml/kg. A further 25 μg/kg of F or 5 μg/kg of S was administered through the side port of the pulmonary arterial catheter introducer 2–3 min before sternotomy. This same dose was repeated with pancuronium (0.05 mg/kg) and lorazepam (0.025 mg/kg) at the start of CPB. If, at any time, SAP increased more than 20% above control, a nitroglycerin (NTG) infusion (50 mg/250 ml) was started. Then, if hypertension was uncontrolled at a rate of 180 drops/min, nitroglycerin infusion was followed by enflurane or halothane in concentrations adequate to return blood pressure to control levels.

CPB was conducted using a Spiraflo BOS-10S oxygenator (Bentley Laboratories Inc., Irvine, CA) with systemic hypothermia (30°C). Myocardial preservation was achieved by intermittent infusion of a cold (4°C) cardioplegic solution (modified Plasma-Lyte, Travenol Laboratories, Deerfield, IL) into the proximal aorta. Protamine (1 mg) to 100 units of heparin was the reversal dose used after CPB. At 15 points during the study, beginning with preoxygenation and concluding 4 hr after entering the SICU, cardiovascular dynamics were recorded. These data included heart rate (HR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), central venous pressure (CVP), cardiac index (CI), mean pulmonary artery pressure (MPAP), pulmonary artery occluded pressure (PAO), cardiac output (CO), stroke index (SI), left ventricle stroke work index (LVSWI), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR). All of the variables were measured except SVR, SI, CI, LVSWI, and PVR, which were individually calculated in the usual manner.

Cardiac output determinations were performed us-

Table 2. Powers of the Between-Drug-Groups ANOVA Test

| Variable name | Estimated population mean | Pooled standard deviation | Lower 95% confidence limit | Upper 95% confidence limit | Detectable difference between means ($\alpha$ = 0.05, $\beta$ = 0.10, power = 0.90) | Difference as percent of population mean |
|---|---|---|---|---|---|---|
| Log D (picograms/ml) | 2.13 | 0.20 | 2.07 | 2.19 | 0.20 | 9.39 |
| Log E (picograms/ml) | 1.91 | 0.26 | 1.83 | 1.99 | 0.25 | 13.09 |
| Log N (picograms/ml) | 2.49 | 0.21 | 2.43 | 2.55 | 0.21 | 8.43 |
| Log SAP (mm Hg) | 2.17 | 0.08 | 2.15 | 2.19 | 0.08 | 3.69 |
| PAO (mm Hg) | 12.58 | 4.55 | 11.25 | 13.91 | 4.46 | 35.45 |
| Log MAP (mm Hg) | 1.97 | 0.08 | 1.95 | 2.00 | 0.08 | 4.06 |
| HR (beats/min) | 67.31 | 11.05 | 64.09 | 70.53 | 10.83 | 16.09 |
| Log CI ($L \cdot min^{-1} \cdot m^{-2}$) | 0.42 | 0.10 | 0.39 | 0.44 | 0.10 | 23.81 |
| Log CO (L/min) | 0.71 | 0.10 | 0.68 | 0.74 | 0.10 | 14.08 |
| DAP (mm Hg) | 69.71 | 14.57 | 65.46 | 73.96 | 14.28 | 20.48 |
| Log CVP (mm Hg) | 0.89 | 0.26 | 0.81 | 0.97 | 0.25 | 28.09 |
| Log SVR (dyne-sec/$cm^5$) | 3.13 | 0.11 | 3.10 | 3.16 | 0.11 | 3.51 |
| Log PVR (dyne-sec/$cm^5$) | 2.05 | 0.24 | 1.98 | 2.12 | 0.24 | 11.71 |
| Log LVSWI ($g \cdot m \cdot beat^{-1} \cdot m^{-2}$) | 1.64 | 0.19 | 1.58 | 1.70 | 0.19 | 11.59 |
| SI ($ml \cdot beat^{-1} \cdot m^{-2}$) | 40.50 | 9.70 | 37.67 | 43.33 | 9.50 | 23.46 |

This table shows that the actual limit of detectable difference was often less than 20% of the normalized data.

ing a thermodilution cardiac output computer (Edwards Laboratories Inc., Santa Ana, CA, model 9520 A); the recorded value consisted of the mean of two consecutive measurements that were within 10% of each other when time allowed (14). At six points in the study, 5 ml of arterial blood was withdrawn and placed in a tube containing EGTA (ethylene-glycol-bis($\beta$-aminoethyl ether)-N,N-tetraacetic acid). The plasma was then separated in a refrigerated centrifuge (International Equipment Company, Needham Heights, MA, model Centra-7R) and stored at −80°C until simultaneous radioenzymatic assays for epinephrine (E), norepinephrine (N), and dopamine (D) levels were made (15). Recovery from surgery was estimated by four measurements: the elapsed time from the end of surgery to the recovery of eyelash reflex, to awakening, to orientation to place, and to extubation.

### *Statistical Methods*

Statistical analyses were performed using Statistical Analysis System Inc. SAS computer software (16). Bartlett's test for homogeneity of variances (17) was performed between the patient drug groups at each time period and over all time periods to determine which variables required log transformation (18) for the analysis of variance (ANOVA) and power calculations. Shapiro and Wilk's *W*-test (19) was then performed on the variables and log-transformed variables to ensure that they were normally distributed. The log transformations and normality tests were performed to fulfill the assumptions of ANOVA (20). The power calculations (Table 2) were performed to determine the smallest difference between the drug group means detectable with the number of patients studied. The estimate of the population mean was calculated from the mean of preinduction control values in all 48 patients (17). The pooled standard deviation was determined by taking the square root of the pooled estimate of common variance from the individual drug group variances, using a procedure described by Colton (21). The upper and lower 95% confidence intervals were calculated by a method that corrected the intervals for sample size by using percentiles of the sampling distribution of *t* (17). The detectable difference was made using a conservative sample size of 20 on an ANOVA power curve found in Dixon and Massey (17, Table A-13). A difference of 20% of the population mean was considered a significant change for each variable. A series of one-way ANOVA calculations with the probability of a type I error set at 0.05 and the probability of a type II error set at 0.10 (17) were performed on each of the variable means between the independent patient drug groups at each time period. Next, one-way repeated measures ANOVA tests for overall differences over time were performed for each patient group using the conservative procedure of Greenhouse and Geisser (22). Differences within each patient group over time were determined by Duncan's Multiple Range Test (23) with Kramer's (24) extension to unequal numbers of replications. To calculate percentage change from control, the means were normalized so that all control

Table 3. Summary of Cardiovascular Dynamics

| | Heart rate (beats/min) | | | | Cardiac output (L/min) | | | | Systemic vascular resistance (dyne sec/cm$^5$) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Event period | Fentanyl mean (SD) | Sufentanil mean (SD) | F | S | Fentanyl mean (SD) | Sufentanil mean (SD) | F | S | Fentanyl mean (SD) | Sufentanil mean (SD) | F | S |
| 1 | 69.23 | 65.69 | | | 5.38 | 5.08 | | | 1367 | 1407 | | |
| | (12.57) | (9.59) | | | (1.10) | (1.18) | | | (324) | (426) | | |
| 2 | 71.09 | 69.65 | | | 5.37 | 6.19 | | [b] | 1304 | 1099[a] | | [b] |
| | (14.15) | (11.35) | | | (1.51) | (1.91) | | | (400) | (373) | | |
| 3 | 69.55 | 68.65 | | | 5.29 | 5.72 | | | 1326 | 1132 | | [b] |
| | (14.62) | (11.46) | | | (1.59) | (1.85) | | | (468) | (370) | | |
| 4 | 66.95 | 69.73 | | | 5.19 | 6.04[a] | | | 1285 | 1035[a] | | [b] |
| | (12.09) | (12.15) | | | (1.42) | (1.65) | | | (404) | (282) | | |
| 5 | 65.91 | 67.00 | | | 4.37 | 5.00 | | | 1663 | 1389[a] | | |
| | (11.35) | (7.96) | | | (1.05) | (1.50) | | | (512) | (468) | | |
| 6 | 64.95 | 70.73 | | | 4.49 | 5.19 | | | 1691 | 1491 | | |
| | (10.48) | (12.25) | | | (1.28) | (2.01) | | | (550) | (480) | | |
| 7 | 62.32 | 72.27[a] | | | 4.40 | 5.03 | | | 1697 | 1526 | | |
| | (10.25) | (12.22) | | | (1.09) | (1.32) | | | (533) | (456) | | |
| 8 | 66.95 | 73.31 | | | 4.55 | 5.02 | | | 1596 | 1453 | | |
| | (12.84) | (13.58) | | | (0.96) | (1.20) | | | (398) | (391) | | |
| 9 | 70.57 | 73.20 | | | 4.44 | 4.82 | | | 1520 | 1381 | | |
| | (11.93) | (11.57) | | | (1.22) | (1.11) | | | (510) | (347) | | |
| 10 | 81.77 | 79.50 | [b] | [b] | 6.39 | 6.90 | [b] | | 927 | 779 | [b] | [b] |
| | (14.10) | (14.28) | | | (1.90) | (1.66) | | | (345) | (184) | | |
| 11 | 80.32 | 81.58 | [b] | [b] | 5.79 | 6.69[a] | [b] | | 1011 | 877 | [b] | [b] |
| | (14.65) | (12.58) | | | (1.07) | (1.58) | | | (376) | (269) | | |
| 12 | 78.59 | 85.38 | [b] | [b] | 5.64 | 6.08 | [b] | | 1140 | 1089 | [b] | [b] |
| | (14.50) | (13.41) | | | (1.68) | (1.79) | | | (520) | (354) | | |
| 13 | 84.86 | 80.77 | [b] | [b] | 5.17 | 5.53 | | | 1387 | 1227 | | |
| | (14.67) | (16.26) | | | (1.29) | (1.42) | | | (543) | (416) | | |
| 14 | 79.00 | 81.54 | [b] | [b] | 5.16 | 5.63 | | | 1394 | 1174[a] | | |
| | (13.89) | (14.40) | | | (1.30) | (1.03) | | | (394) | (340) | | |
| 15 | 83.20 | 83.42 | [b] | [b] | 5.15 | 5.32 | | | 1326 | 1197 | | |
| | (14.47) | (15.51) | | | (1.29) | (1.04) | | | (377) | (412) | | |

Abbreviations: F, fentanyl patient group; S, sufentanil patient group. [a]Indicates a significant difference between the patient drug groups at $P < 0.05$. [b]Indicates a significant difference from pre-induction control means ($P < 0.05$) by the procedure described by Greenhouse and Geisser (21). Event periods are shown in Table 9.

levels were 0.00% for each patient. Analysis of variance was performed on the transformed data. The variables of time to recovery of eyelash reflex, to awakening, to patient orientation, and to extubation were tested by the Kruskal–Wallis Rank Sum statistic with correction for ties (25). At each event the percent of the total number of patients with the incidence of either systolic hypertension, diastolic hypertension, or tachycardia was compared in both groups, using the Fisher exact probability test (26). Differences were considered statistically significant if the exact probability test value was less than or equal to 0.05. Cardiovascular dynamic values are reported as means with standard deviations (SD), and catecholamine values are presented as means and standard error of the mean (SEM). Recovery from surgery values are reported as median times.

## Results

Shapiro and Wilk's normality W-test and Barlett's homogeneity of variance test for the 15 time periods determined that the variables D, E, N, SAP, MAP, CO, CI, CVP, SVR, PVR, and LVSWI required log transformation to achieve normal distributions and equality of variances in both patient groups. Only the variable MPAP could not be normalized at all time periods by log transformation and therefore is not reported. The variable CVP did not achieve equality of variance over the 15 time periods, even with log transformation, although log transformation did achieve homogeneity of variance between the drug groups at each time period. We considered a difference between the drug groups equal to 20% of the population mean to be clinically significant. Table 2

Table 4. Summary of Cardiovascular Dynamics

| | Mean arterial pressure (mm Hg) | | Systolic arterial pressure (mm Hg) | | Diastolic arterial pressure (mm Hg) | |
|---|---|---|---|---|---|---|
| Event Period | Fentanyl mean (SD) | Sufentanil mean (SD) | Fentanyl mean (SD) | Sufentanil mean (SD) | Fentanyl mean (SD) | Sufentanil mean (SD) |
| 1 | 98.05 | 93.38 | 153.5 | 146.4 | 70.36 | 69.15 |
| | (17.97) | (16.88) | (30.2) | (22.8) | (15.30) | (13.93) |
| 2 | 92.23 | 87.78 | 139.3 | 134.8 | 68.73 | 64.27 |
| | (20.84) | (19.94) | (30.7) | (32.0) | (16.76) | (15.35) |
| 3 | 89.31 | 83.88 | 135.0 | 127.4 | 66.50 | 62.12 |
| | (18.77) | (17.78) | (26.8) | (28.2) | (15.83) | (13.74) |
| 4 | 86.99 | 82.71 | 133.6 | 125.2 | 63.64 | 61.50 |
| | (15.04) | (14.53) | (24.0) | (24.9) | (11.78) | (11.21) |
| 5 | 92.66 | 88.50 | 137.5 | 130.7 | 70.27 | 67.38 |
| | (12.67) | (14.06) | (18.1) | (22.5) | (11.85) | (11.28) |
| 6 | 94.49 | 96.31 | 141.9 | 141.5 | 70.77 | 73.69 |
| | (11.49) | (16.89) | (16.6) | (26.5) | (11.58) | (14.10) |
| 7 | 95.02 | 97.98 | 142.5 | 146.3 | 71.27 | 73.85 |
| | (15.73) | (16.84) | (17.9) | (24.1) | (15.71) | (14.56) |
| 8 | 94.26 | 93.93 | 140.8 | 141.2 | 71.00 | 70.31 |
| | (14.59) | (11.37) | (17.1) | (19.1) | (14.57) | (9.45) |
| 9 | 84.88 | 86.94 | 126.5 | 128.9 | 64.09 | 66.36 |
| | (13.69) | (11.68) | (21.3) | (19.4) | (12.97) | (11.01) |
| 10 | 77.78 | 76.87 | 119.4 | 114.5 | 56.95 | 58.08 |
| | (9.19) | (10.46) | (15.7) | (14.7) | (7.80) | (9.43) |
| 11 | 79.13 | 81.14 | 120.1 | 121.8 | 58.68 | 61.08 |
| | (11.33) | (12.16) | (18.7) | (16.6) | (9.53) | (11.00) |
| 12 | 85.20 | 88.46 | 124.5 | 127.9 | 65.59 | 68.73 |
| | (14.69) | (9.38) | (19.9) | (16.6) | (13.92) | (8.51) |
| 13 | 96.86 | 91.73 | 139.0 | 132.5 | 75.86 | 71.35 |
| | (22.68) | (15.58) | (32.7) | (25.2) | (19.42) | (15.25) |
| 14 | 98.37 | 91.07 | 138.8 | 131.7 | 78.15 | 70.77 |
| | (13.65) | (14.04) | (19.4) | (21.8) | (12.48) | (13.23) |
| 15 | 94.59 | 88.42 | 135.5 | 126.1 | 74.15 | 69.58 |
| | (15.92) | (13.61) | (22.4) | (21.0) | (14.09) | (12.32) |

Symbols are the same as those described in Table 3. Event periods are described in Table 9.

indicates the difference between drug groups that could be detected with a power of 0.90 for the coronary artery surgery population. In only four incidences was this difference above 20% of the population mean. A difference of 35% could be detected for the variable PAO, log CI showed a 24% difference, log CVP showed a 28% difference, and SI showed a difference of 23% of the population mean.

There were no statistically significant differences in demographic data between either of the groups (Table 1) except age when separated by sex. When sex was not considered, age was no longer significantly different. Fisher's exact test determined that there was no difference between the groups for the number of patients taking propranolol (S, $^{16}/_{26}$; F, $^{12}/_{22}$). Analysis of variance revealed that there also was no difference between the patient groups for the daily propranolol dose (S, 178 ± 83 mg/day; F, 177 ± 78 mg/day). Analysis of variance indicated that there were no significant differences in presurgical hemodynamic and catecholamine status between the patients given S and patients given F. This applied equally whether the patients were or were not taking $\beta$-adrenergic inhibitors before surgery.

Tables 3, 4, 5, and 6 summarize the cardiovascular data. No statistically significant differences were found between treatment groups with respect to duration of anesthesia or surgery. In general, catecholamine concentrations and hemodynamic responses remained stable during induction of anesthesia and prior to sternotomy. However, there was a significant difference (Table 7) in mean HR between the patient groups 2 min after sternotomy (S, 72.3; F, 62,3; $P$ = 0.0041). When HR was normalized as percent change from control levels, the mean percent change from control was greater with S than with F during sternotomy (S, 9.00%; F, −4.13%; $P$ = 0.0257), 2 min after sternotomy (S, 12.03%; F, −8.42%; $P$ = 0.0013), 5 min after sternotomy (S, 12.61%; F, −1.75%; $P$ = 0.0155), and during chest closure (S, 31.40%; F, 16.23%;

Table 5. Summary of Cardiovascular Dynamics

| | Cardiac index (L·min$^{-1}$·m$^{-2}$) | | | | LVSWI (g-m·beat$^{-1}$·m$^{-2}$) | | Stroke index (ml·beat$^{-1}$·m$^{-2}$) | |
|---|---|---|---|---|---|---|---|---|
| Event period | Fentanyl mean (SD) | Sufentanil mean (SD) | F | S | Fentanyl mean (SD) | Sufentanil mean (SD) | Fentanyl mean (SD) | Sufentanil mean (SD) |
| 1 | 2.817<br>(0.495) | 2.545<br>(0.580) | | | 51.24<br>(21.23) | 44.02<br>(16.48) | 41.72<br>(9.62) | 39.48<br>(9.76) |
| 2 | 2.792<br>(0.586) | 3.087<br>(0.902) | | [b] | 44.87<br>(15.16) | 45.29<br>(16.27) | 40.06<br>(9.17) | 44.53<br>(10.85) |
| 3 | 2.796<br>(0.777) | 2.850<br>(0.877) | | [b] | 45.90<br>(22.28) | 40.10<br>(14.48) | 41.99<br>(15.58) | 41.16<br>(10.70) |
| 4 | 2.734<br>(0.697) | 3.017<br>(0.790) | | | 42.61<br>(14.65) | 41.85<br>(9.15) | 40.88<br>(10.97) | 44.14<br>(8.65) |
| 5 | 2.291<br>(0.508) | 2.508<br>(0.729) | [b] | | 41.19<br>(14.95) | 38.72<br>(11.74) | 36.02<br>(10.68) | 37.68<br>(10.44) |
| 6 | 2.349<br>(0.615) | 2.588<br>(0.909) | [b] | | 48.61<br>(36.33) | 41.85<br>(13.63) | 39.60<br>(17.45) | 37.31<br>(13.42) |
| 7 | 2.304<br>(0.513) | 2.525<br>(0.640) | [b] | | 44.01<br>(13.46) | 40.78<br>(11.58) | 37.57<br>(8.77) | 35.55<br>(9.47) |
| 8 | 2.384<br>(0.439) | 2.520<br>(0.597) | | | 41.75<br>(11.98) | 38.97<br>(11.06) | 36.48<br>(7.89) | 35.26<br>(9.50) |
| 9 | 2.345<br>(0.704) | 2.419<br>(0.604) | [b] | | 33.73<br>(11.95) | 35.61<br>(12.63) | 34.33<br>(12.22) | 33.62<br>(9.19) |
| 10 | 3.349<br>(0.966) | 3.445<br>(0.757) | | [b] | 36.76<br>(18.26) | 36.94<br>(13.27) | 41.85<br>(13.19) | 44.73<br>(14.30) |
| 11 | 3.047<br>(0.595) | 3.333<br>(0.675) | | [b] | 35.30<br>(16.08) | 36.16<br>(9.58) | 39.45<br>(12.05) | 41.83<br>(11.55) |
| 12 | 2.963<br>(0.851) | 3.044<br>(0.864) | | [b] | 36.97<br>(11.94) | 35.52<br>(9.74) | 38.57<br>(11.60) | 36.23<br>(10.46) |
| 13 | 2.706<br>(0.704) | 2.764<br>(0.682) | | | 36.77<br>(14.41) | 37.62<br>(15.37) | 32.17<br>(8.51) | 35.22<br>(10.19) |
| 14 | 2.674<br>(0.634) | 2.813<br>(0.461) | | | 39.94<br>(15.75) | 37.79<br>(11.49) | 34.77<br>(10.92) | 35.73<br>(9.29) |
| 15 | 2.663<br>(0.604) | 2.685<br>(0.476) | | | 35.43<br>(12.73) | 33.49<br>(9.66) | 32.73<br>(9.33) | 33.20<br>(8.18) |

Symbols are the same as those described in Table 3. Event periods are described in Table 9. LVSWI, left ventricle stroke work index.

$P = 0.0358$). As seen in Figure 1, S was also associated with a greater frequency of HR, above 95 beats/min at these events than was F.

Statistically significant differences calculated from the log of CO between the patient groups occurred 2 min after intubation (S, 6.04; F, 5.19) and 5 min after protamine was given (S, 6.69; F, 5.79; Table 7). Calculation of percent change from control showed that the patients given S had significantly greater percent change in CO 1 min after induction (S, 27.31%; F, 0.18%; $P = 0.0191$), 2 min after intubation (S, 24.57%; F, −2.12%; $P = 0.0178$), prior to skin incision (S, 1.94%; F, −17.52%; $P = 0.0225$), during sternotomy (S, 4.65%; F, −15.00%; $P = 0.0331$), 2 min after sternotomy (S, 2.43%; F, −16.32%; $P = 0.0109$), 5 min after sternotomy (S, 3.35%; F, −12.65%; $P = 0.0423$), and 5 min after protamine (S, 42.56%; F, 12.02%; $P = 0.05$).

Neither log MAP, DAP nor log SAP was statistically significantly different in the two groups (Table 4). Patients given S had significantly lower (Table 7) log transformed SVR 1 min after induction (S, 1099; F, 1304), 2 min after intubation (S, 1035; F, 1285), prior to skin incision (S, 1389; F, 1663), and in the second postoperative hour (S, 1174; F, 1394). The normalized percent changes in SVR from control levels mirrored these results for three of the time periods, e.g., SVR changes 1 min after induction (S, −18.40%; F, −1.78%; $P = 0.0457$); 2 min after intubation (S, −22.78%; F, −1.00%, $P = 0.0202$); and after 2 hr in the SICU (S, −11.68%; F, 9.90%; $P = 0.0255$). The PAO, log CVP, and log CI means were not statistically significantly different between the two patient groups at any time. During chest closure (Table 7), log PVR levels were significantly lower for patients given S (S, 96.35 125.23), although this difference was less than 20% of the population mean.

To investigate changes from control values and interrelationships between HR, CO, and SVR (Table 3), one-way repeated measures ANOVA for each patient

Table 6. Summary of Cardiovascular Dynamics

| | Pulmonary artery occluded pressure (mm Hg) | | | | Central venous pressure (mm Hg) | | | | Pulmonary vascular resistance (dyne-sec/cm$^5$) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Event period | Fentanyl mean (SD) | Sufentanil mean (SD) | F | S | Fentanyl mean (SD) | Sufentanil mean (SD) | F | S | Fentanyl mean (SD) | Sufentanil mean (SD) | F | S |
| 1 | 12.64 | 12.54 | | | 8.273 | 10.346 | | | 113.4 | 144.3 | | |
| | (4.49) | (4.61) | | | (4.366) | (8.989) | | | (93.3) | (69.5) | | |
| 2 | 11.64 | 12.81 | | | 8.318 | 8.308 | | | 103.2 | 105.6 | | |
| | (4.57) | (4.69) | | | (3.657) | (3.761) | | | (60.2) | (46.0) | | |
| 3 | 11.73 | 12.46 | | | 8.046 | 8.654 | | | 94.5 | 118.0 | | |
| | (5.02) | (4.68) | | | (3.359) | (3.959) | | | (66.5) | (77.2) | | |
| 4 | 11.59 | 12.04 | | | 8.546 | 8.654 | | | 95.1 | 93.3 | | |
| | (4.84) | (4.40) | | | (4.217) | (3.199) | | | (61.5) | (36.1) | | |
| 5 | 11.00 | 12.15 | | | 7.000 | 8.846 | | | 107.9 | 98.5 | | |
| | (3.74) | (3.40) | | | (2.879) | (4.047) | | | (47.6) | (50.5) | | |
| 6 | 10.68 | 11.69 | | | 6.455 | 8.423$^a$ | | | 117.7 | 114.4 | | |
| | (3.76) | (2.92) | | | (3.218) | (3.859) | | | (71.0) | (54.5) | | |
| 7 | 10.86 | 12.15 | | | 7.273 | 7.615 | | | 134.9 | 108.4 | | |
| | (3.94) | (3.84) | | | (3.341) | (3.176) | | | (64.5) | (55.9) | | |
| 8 | 12.00 | 11.62 | | | 6.818 | 7.308 | | | 117.3 | 108.3 | | |
| | (5.06) | (3.83) | | | (3.065) | (2.853) | | | (78.3) | (54.9) | | |
| 9 | 10.30 | 9.76 | | $^b$ | 5.950 | 7.480 | | | 99.5 | 100.9 | | |
| | (4.47) | (3.55) | | | (2.874) | (3.280) | | | (50.7) | (37.4) | | |
| 10 | 16.77 | 16.00 | | $^b$ | 10.000 | 12.269 | | $^b$ | 96.5 | 101.6 | | |
| | (71.0) | (5.33) | | | (4.163) | (4.721) | | | (51.6) | (59.9) | | |
| 11 | 15.36 | 16.62 | | $^b$ | 10.182 | 11.885 | | | 130.9 | 95.8 | | |
| | (5.39) | (4.85) | | | (4.350) | (4.910) | | | (102.8) | (57.7) | | |
| 12 | 15.18 | 15.54 | | $^b$ | 12.182 | 12.462 | $^b$ | $^b$ | 125.2 | 96.4$^a$ | | |
| | (5.33) | (3.99) | | | (5.039) | (3.860) | | | (66.5) | (80.8) | | |
| 13 | 14.40 | 14.12 | | | 13.500 | 12.615 | $^b$ | $^b$ | 111.8 | 115.5 | | |
| | (4.32) | (3.97) | | | (4.651) | (3.419) | | | (70.2) | (60.0) | | |
| 14 | 14.84 | 12.62 | | | 13.526 | 11.885 | $^b$ | $^b$ | 124.7 | 119.8 | | |
| | (5.55) | (4.71) | | | (4.155) | (3.973) | | | (70.7) | (71.0) | | |
| 15 | 14.42 | 13.63 | | | 13.579 | 13.208 | $^b$ | $^b$ | 142.1 | 145.4 | | |
| | (5.40) | (4.53) | | | (3.079) | (3.788) | | | (50.4) | (94.5) | | |

Symbols are the same as those described in Table 3. Event periods are described in Table 9.

Table 7. ANOVA Summary Table

| Source | Event period | F test value | P value | Fentanyl mean (SD) | Sufentanil mean (SD) |
|---|---|---|---|---|---|
| Log D | 12 | 5.03 | 0.0337 | 2.3499 | 2.1603 |
| | | | | (0.252) | (0.192) |
| Heart rate | 7 | 9.14 | 0.0041 | 62.32 | 72.27 |
| | | | | (10.25) | (12.22) |
| Log CO | 4 | 4.41 | 0.0413 | 0.7007 | 0.7676 |
| | | | | (0.1152) | (0.1055) |
| Log CO | 11 | 4.68 | 0.0358 | 0.7545 | 0.8144 |
| | | | | (0.0927) | (0.0981) |
| Log CVP | 6 | 4.08 | 0.0494 | 0.744 | 0.882 |
| | | | | (0.270) | (0.203) |
| Log SVR | 2 | 4.05 | 0.0500 | 3.097 | 3.016 |
| | | | | (0.127) | (0.152) |
| Log SVR | 4 | 5.45 | 0.0240 | 3.088 | 2.997 |
| | | | | (0.138) | (0.131) |
| Log SVR | 5 | 4.10 | 0.0486 | 3.202 | 3.118 |
| | | | | (0.131) | (0.153) |
| Log SVR | 14 | 4.24 | 0.0455 | 3.129 | 3.053 |
| | | | | (0.120) | (0.123) |
| Log PVR | 12 | 5.33 | 0.0255 | 2.053 | 1.899 |
| | | | | (0.195) | (0.256) |

Event periods are the same as those described in Table 9. Abbreviations: D, dopamine concentration (picograms/ml); CO, cardiac output; CVP, central venous pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; (SD), standard deviation.

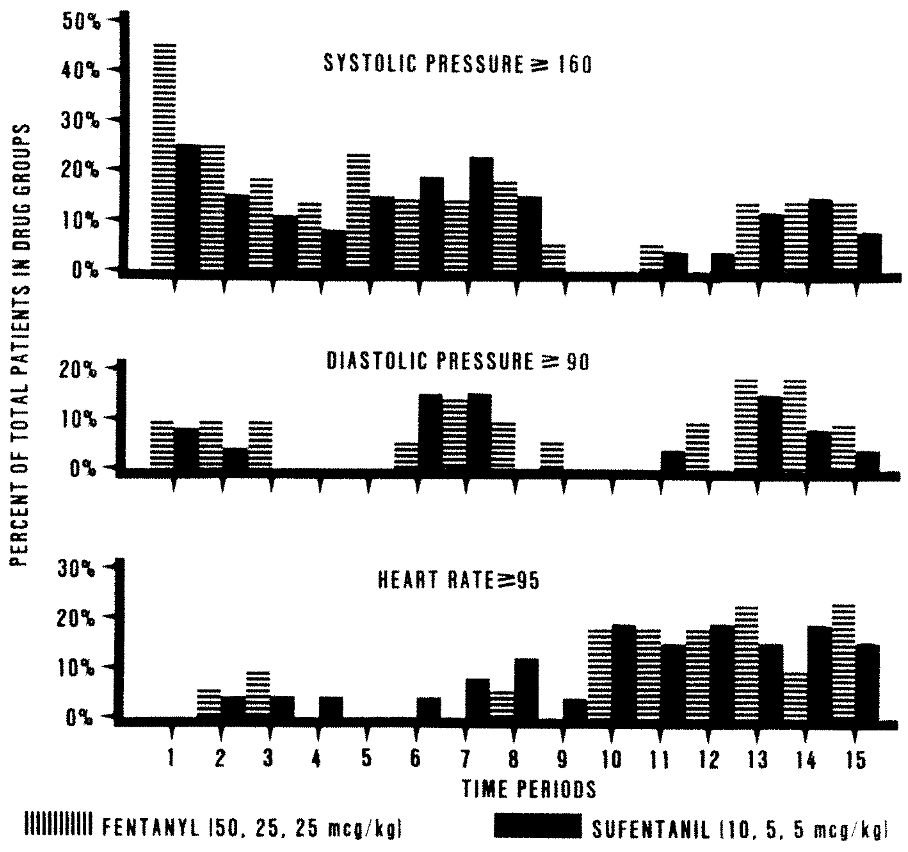


Figure 1. Representation of the percent of the patients in both drug groups that exceeded the criteria indicated. Analysis by Fisher's exact test showed there were no significant differences between the two narcotics during the anesthetic and the early postoperative course. The event times are the same as in Table 9.

drug group over time was performed using the conservative procedure of Greenhouse and Geisser (22). When the ANOVA indicated that there were significant changes, Duncan's Multiple Range Test (23) with Kramer's (24) extension to unequal numbers of replications determined which mean values were significantly different from preinduction control levels. This analysis disclosed that patients given S had significantly higher HR and CO (or CI) 2 min after protamine, 5 min after protamine, and during chest closure, correlating with significantly lower levels of SVR. In contrast, patients given F did not have these changes because CO did not change significantly from the control at any time measured. When S was given, SVR was significantly reduced from the control during induction with simultaneously elevated CI, but HR remained at control levels.

Induction of anesthesia was associated with a reduction in plasma catecholamine levels in both narcotic groups. However, there were no statistically significant differences between the two narcotics in any of the catecholamine levels (Fig. 2), except that the level of D during chest closure (Table 7) was significantly lower with S than with F (S, 156.3; F, 271.3). There was also an increase in plasma levels of all catecholamines during bypass, the greatest increase in the N level. When the ANOVA procedure of Greenhouse and Geisser (22) was used, the E concentration significantly increased above the control level during CPB only in patients given S. In contrast, the N concentration significantly increased above the control level during CPB only in patients given F (22).

Proportional analysis was performed on hypertension and tachycardia using the Fisher exact probability test (26). Comparisons were made between the percent of patients within each drug group with the incidence of either hypertension or tachycardia (Fig. 1). There was no statistical difference between the drug groups at any time, based upon the criteria shown in Figure 1. Comparison of blood pressure increase exceeding 20% of control between the narcotic groups reached statistical significance in the fourth postoperative hr, when more patients given F (18%, $^{4}/_{22}$) had blood pressure increases compared to patients given S (0%, $P < 0.05$) (26).

Four of the F-treated group and seven of the S-treated group had NTG administered intraoperatively during at least one measurement period. Initiation of NTG treatment was influenced more by the SAP exceeding 160 mm Hg than by the protocol's criterion of 20% SAP increase over control. Inhalational supplementation of anesthesia was necessary in four patients in each group. Postoperatively six of the F-treated group and eight of the S-treated group required NTG

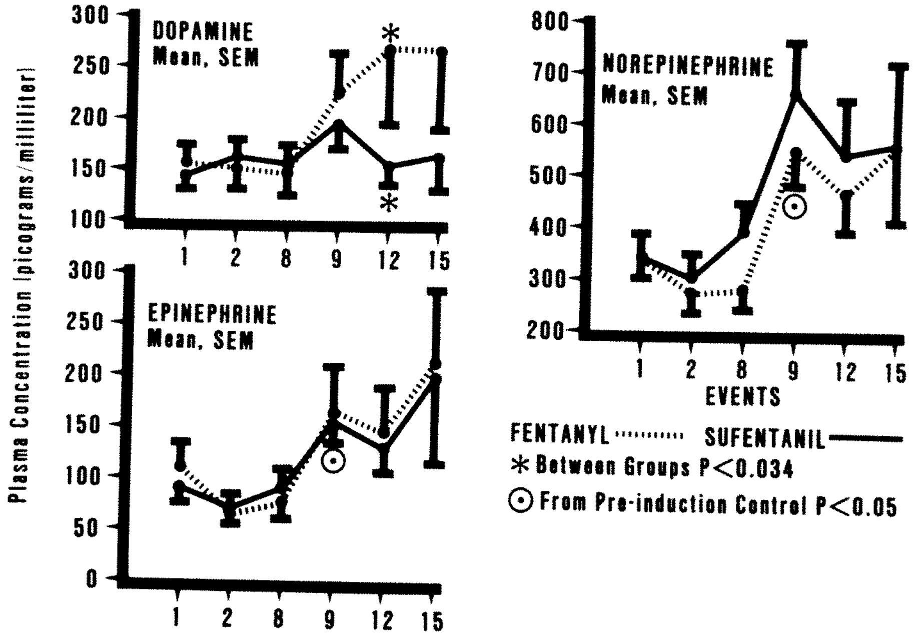


Figure 2. Comparison of the initial catecholamine levels and response of patients undergoing cardiac surgery with either fentanyl or sufentanil anesthesia. The numbers representing events can be referred to in Table 9.

within 3 hr of their admission to the SICU. There was no statistically significant difference between the two groups in the frequency with which intraoperative (S, 27%; F, 18%) or postoperative (S, 31%; F, 27%) vasoactive agents were used (26).

The median time from induction to loss of eyelash reflex was shorter for the patients given S than for the patients given F (median time (in min): S, 1.4; F, 2.0; $P = 0.07$). Times for recovery from surgery were comparable in the two groups. No statistically significant differences in recovery were found between the two groups (Table 8). There was no evidence of recall in either patient group.

Table 8. Comparison of Recovery Times

| Parameter | Fentanyl | Sufentanil |
|---|---|---|
| Recovery of eyelash reflex (hr) | | |
| Median | 4.3 | 4.6 |
| Min | 0.1 | 0.3 |
| Max | 19.8 | 14.0 |
| Time to awake (hr) | | |
| Median | 5.3 | 6.5 |
| Min | 1.9 | 0.3 |
| Max | 19.8 | 16.0 |
| Time to orientation (hr) | | |
| Median | 6.1 | 7.1 |
| Min | 1.9 | 1.6 |
| Max | 19.8 | 23.1 |
| Time to extubation (hr) | | |
| Median | 18.5 | 17.0 |
| Min | 9.7 | 4.3 |
| Max | 58.3 | 88.0 |

No significant difference could be detected by the Kruskal–Wallis Rank Sum Statistic.

## Discussion

Large doses of S (40 $\mu g \cdot kg^{-1} \cdot min^{-1}$) are associated with minimal changes in cardiovascular hemodynamics in atropinized dogs (27), suggesting that S might be suitable for use as a complete anesthetic in humans. The present study indeed confirms that good cardiovascular stability is obtained with S, a conclusion that is in agreement with other workers who have used S in this manner (5–8). We find that S does decrease SVR at more events than does F, but other differences in cardiovascular stability are difficult to demonstrate between the two drugs.

A double-blind comparison of S (2 μg/kg) and F (20 μg/kg) used as a supplement to balanced anesthesia failed to distinguish between the two drugs from the view of cardiovascular and catecholamine responses (28). In balanced anesthesia not involving cardiac surgery, Kalenda and Scheijgrond found, in comparing F and S, that SAP and HR were similar with both drugs (29). The data reported by De Lange et al. (13) suggest that cardiovascular stability, with respect to a lesser increase in HR after sternotomy hypertension, is better with S than with F. Contrary to the findings of Khoury et al. (6), we did not find any significant increases in HR with S because of the use of pancuronium. Pancuronium was given simultaneously with the narcotics, and our pancuronium dose (0.1 mg/kg) was slightly lower than that used by Khoury et al. (0.12 mg/kg).

Table 9. Event Periods

| Event period | Event |
|---|---|
| 1 | Preinduction control |
| 2 | One minute after induction |
| 3 | One minute after intubation |
| 4 | Two minutes after intubation |
| 5 | Prior to skin incision |
| 6 | Sternotomy |
| 7 | Two minutes after sternotomy |
| 8 | Five minutes after sternotomy |
| 9 | Five minutes into cardiopulmonary bypass |
| 10 | Two minutes after protamine |
| 11 | Five minutes after protamine |
| 12 | Chest closure |
| 13 | Entry into the surgical intensive care unit |
| 14 | Two hours into the surgical intensive care unit |
| 15 | Four hours into the surgical intensive care unit |

Even when considering the peripheral vasodilatory effects of protamine, it should be noted that a pattern of significantly reduced SVR with simultaneous elevations in CO (or CI) and HR above control levels was better maintained with S in the time between protamine administration and chest closure. Patients given F exhibited transitory reduced SVR with simultaneous elevations in CI and HR above control levels only 2 min after protamine (Table 3). These observations suggest that anesthesia with high doses of S may have a vasodilatory effect, a characteristic that was seen during induction, after protamine administration, and in the SICU, when a significantly lower SVR was found in the S-treated group. However, the induction hemodynamics could have been entirely due to the fact that S was a more potent drug administered in a smaller volume.

Our results with regards to catecholamine reponse differ from those described by Sebel et al. (10). They found marked (5–10-fold) elevations of catecholamine concentrations during bypass and in the early postoperative period, while our results were less striking (2–4-fold). In our study, no significant differences in plasma E or N levels were found in the two groups prior to CPB, results that are in agreement with those reported by Murkin et al. (30). As seen in Figure 2, mean E and N concentrations approximately doubled, from 5 min after sternotomy to 5 min into CPB. This may reflect a change in stress hormone release after CPB or very low levels of narcotic left in the central nervous system. The techniques of narcotic administration and neuromuscular blockade used in our study are comparable to Sebel et al. (10) and Bovill et al. (11), except that we used a slightly different dosing schedule (Sebel: 12, 3, and 7 μg/kg; Bovill: 12, 3, and 5 μg/kg; Howie: 10, 5, and 5 μg/kg), perhaps allowing maintenance of higher levels of S during these stress periods. Differences in catecholamine concentrations may be entirely due to small variations in techniques of narcotic administration or surgical manipulation. The higher D levels found during chest closure in F patients was not due to the use of dobutamine as its administration had been carefully excluded in the patients reported here. The mechanism for this significant difference in D levels between F and S patients cannot be explained by our methods of investigation. No morbidity findings could be attributed to any catecholamine changes with either drug.

The electroencephalographic effect of S has been found to be indistinguishable from that of F (31,32). This suggests that the two agents have very similar actions on the central nervous system. We found no instance of awareness during our study and felt that both S and F in combination with lorazepam provided adequate anesthesia for cardiac surgery. Like De Lange et al. (13), we were unable to distinguish any differences in recovery in patients given F or S.

Although sufentanil is 5–10 times more potent than fentanyl (1), it appears to have similar effects on cardiovascular dynamics, metabolic responses to surgery, and neurophysiological effects. Only during sternotomy was sufentanil control of blood pressure less evident than fentanyl control, by the criteria in Figure 1. Because S can reduce SVR better than F, allocating more of the total dose of narcotic for sternotomy and raising the drug plasma concentration at this point may improve the control of hypertension (33).

The authors wish to thank Dr. Peter S. Sebel for his advice in the preparation of this manuscript and Dr. Gerard S. Kakos for his cooperation and permission to study his patients.

## References

1. De Castro J, Van De Water A, Wouters L, Xhonneux R, Reneman R, Kay B. A comparative study of cardiovascular, neurological and metabolic side effects of eight narcotics in dogs. Acta Anaesthesiol Belg 1979;30:5–99.
2. Niemegeers CJE, Schellekins KHL, van Bever WFM, Janssen PAJ. Sufentanil, a very potent and extremely safe intravenous morphine-like compound in mice, rats, and dogs. Arzneim Forsch 1976;26(8):1551–6.
3. Colpaert FC, Neimegeers CJE, Janssen PAJ, van Ree J. Narcotic cueing properties of intraventricularly administered sufentanil, fentanyl, morphine and met-enkephalin. Eur J Pharmacol 1978;47:115–9.
4. van Bever WFM, Niemegeers CJE, Schellekens KHL, Janssen PAJ. N-4-substituted 1-(2-arylethyl)-4-piperidinyl-N-phenylpropanamides, a novel series of extremely potent analgesics with unusually high safety margin. Arzneim Forsch 1976;26:1548–51.

5. Griesemer RW, Moldenhaurer CC, Hug CC Jr., Holbrook GW. Sufentanil anesthesia for aortocoronary bypass surgery: 30 μg/kg vs 15 μg/kg. Anesthesiology 1982;57:A48.
6. Khoury GF, Estafanous FG, Zurick AM, Lytle B. Sufentanil/pancuronium vs sufentanil/metocurine anesthesia for coronary artery surgery. Anesthesiology 1982;57:A47.
7. Dubois-Primo J, Geens-Bastenier J, Genicot C. The use of fentanyl and sufentanil (R30,730) for analgesic anesthesia during cardiac surgery with extracorporeal circulation: a double blind study. Anesthesie Reanimation Pratique 1976;6:175–9.
8. Sebel PS, Bovill JG. Cardiovascular effects of sufentanil anesthesia: a study in patients undergoing cardiac surgery. Anesth Analg 1982;61:115–9.
9. De Castro J. Practical applications and limitations of analgesic anesthesia. A review. Acta Anaesthesiol Belg 1976;27:107–28.
10. Sebel PS, Bovill JG, Fiolet JWT, Touben JL, Philbin DM. Hormonal effects of sufentanil anesthesia. Anesth Analg 1982;61:214–5.
11. Bovill JG, Sebel PS, Fiolet JWT, Touber JL, Kok K, Philbin DM. The influence of sufentanil on endocrine and metabolic responses to cardiac surgery. Anesth Analg 1983;62:391–7.
12. Rosow CE, Philbin DM, Moss J, Keegan CR, Schneider RC. Sufentanil vs fentanyl: I. Suppression of hemodynamic responses. Anesthesiology 1983;59:A323.
13. De Lange S, Boscoe MJ, Stanley TH, Pace N. Comparison of sufentanyl-$O_2$ and fentanyl-$O_2$ for coronary artery surgery. Anesthesiology 1982;56:112–8.
14. Forrester JS, Ganz W, Diamond G, McHugh T, Chonette DW, Swan HJC. Thermodilution cardiac output determination with a single flow-directed catheter. Am Heart J 1972;83:306–11.
15. Peuler JD, Johnson GA. Simultaneous single isotope radioenzymatic assay of plasma norepinephrine, epinephrine, and dopamine. Life Sci 1977;21:625–36.
16. Helig JT, Council KA, eds. SAS users guide, 1979. Raleigh, North Carolina: SAS Institute, Inc, 1979:237–63, 427–32.
17. Dixon WJ, Massey FJ Jr. Introduction to statistical analysis (3rd ed). New York: McGraw-Hill Book Company, 1969:77–83, 277–9, 308–10, 464, 521, 524.
18. Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983;286:1489–93.
19. Shapiro SS, Wilk MB. An analysis of variance test for normality. Biometrika 1965;52:591–611.
20. Eisenhart C. The assumptions underlying the analysis of variance. Biometrics 1947;3:1–21.
21. Colton T. Statistics in medicine. Boston: Little Brown and Company, 1974:136–46.
22. Greenhouse SW, Geisser S. On methods in analysis of profile data. Psychometrika 1959;24:95–112.
23. Duncan DB. Multiple range and multiple F tests. Biometrics 1955;11:1–42.
24. Kramer CY. Extension of multiple range tests to group means with unequal numbers of replications. Biometrics 1956;12:307–10.
25. Hollander M, Wolfe DA. Nonparametric Statistical Methods. New York: Wiley and Sons, 1973:114–9.
26. Finney DJ, Latscha R, Bennett BM, Hsu P. Tables for testing signficance in a 2 × 2 contingency table. London: Cambridge University Press, 1963:46–51,Table 1.
27. Reddy P, Liu W-S, Port D, Gillmore S, Stanley TH. Comparison of haemodynamic effects of anaesthetic doses of alphaprodine and sufentanil in the dog. Can Anaesth Soc J 1980;27:345–50.
28. Rolly G, Kay B, Cockx F. A double blind comparison of high doses of fentanyl and sufentanil in men: influence on cardiovascular, respiratory and metabolic parameters. Acta Anaesthiol Belg 1979;30:247–54.
29. Kalenda Z, Scheijgrond HW. Anaesthesia with sufentanil-analgesia in carotid and vertebral arteriography. A comparison with fentanyl. Anaesthesist 1976;25:380–3.
30. Murkin JM, Moldenhauer CC, Griesemer RW, Hug CC. Fentanyl vs sufentanil: comparison of hemodynamic and catecholamine responses during coronary artery surgery. Sixth Annual Meeting of the Society of Cardiovascular Anesthesiologists. London: Academic Press, 1984:100–1.
31. Bovill JG, Sebel PS, Waugnier A, Rog P. Electroencephalographic effects of sufentanil anesthesia in man. Br J Anaesth 1982;54:45–52.
32. Sebel PS, Bovill JG, Waugnier A, Rog P. Effects of high dose fentanyl anesthesia on the electroencephalogram. Anesthesiology 1981;55:203–11.
33. Howie MB, Smith DF, Dasta JF, Harrington K, Reitz J. Pharmacokinetic comparison of sufentanil and fentanyl during anesthesia for cardiac surgery. Anesthesiology 1984;61:A377.

ANESTH ANALG
1985;64:888–96

# Intraoperative Changes in Blood Coagulation and Thrombelastographic Monitoring in Liver Transplantation

Yoo Goo Kang, MD, Douglas J. Martin, MD, Jose Marquez, MD, Jessica H. Lewis, MD, Franklin A. Bontempo, MD, Byers W. Shaw Jr, MD, Thomas E. Starzl, MD, and Peter M. Winter, MD

KANG YG, MARTIN DJ, MARQUEZ J, LEWIS JH, BONTEMPO FA, SHAW BW Jr, STARZL TE, WINTER PM: Intraoperative changes in blood coagulation and thrombelastographic monitoring in liver transplantation. Anesth Analg 1985;64:888–96.

*The blood coagulation system of 66 consecutive patients undergoing consecutive liver transplantations was monitored by thrombelastograph and analytic coagulation profile. A poor preoperative coagulation state, decrease in levels of coagulation factors, progressive fibrinolysis, and whole blood clot lysis were observed during the preanhepatic and anhepatic stages of surgery. A further general decrease in coagulation factors and platelets, activation of fibrinolysis, and abrupt decrease in levels of factors V and VIII occurred before and with reperfusion of the homograft. Recovery of blood coagulability began 30–60 min after reperfusion of the graft liver, and coagulability had returned toward baseline values 2 hr after reperfusion. A positive correlation was shown between the variables of thrombelastography and those of the coagulation profile. Thrombelastography was shown to be a reliable and rapid monitoring system. Its use was associated with a 33% reduction of blood and fluid infusion volume, whereas blood coagulability was maintained without an increase in the number of blood product donors.*

Key Words: BLOOD—coagulation. LIVER—transplantation.

Liver transplantation, which began as highly experimental surgery 20 yr ago, is now recognized as a major means of therapy for patients with end-stage liver disease (1). However, massive blood loss during liver transplantation is still a major concern. The liver produces most of the blood coagulation factors, so it is not surprising that we see very low levels of these factors and prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT) in many patients receiving liver transplants (2). Frequently we have seen thrombocytopenia, which may result from gastrointestinal bleeding, splenomegaly, or malnutrition (3). At the same time, numerous collateral channels and portal hypertension, together with increased capillary fragility, make maintenance of surgical hemostasis very difficult.

Previous studies on the blood coagulation system in humans and in animals undergoing liver transplantation have demonstrated dilutional coagulopathy associated with massive blood transfusion, decreased fibrinogen levels, and thrombocytopenia (4,5). Fibrinolysis, beginning during the anhepatic stage of surgery and becoming "explosive" on reperfusion of the homograft, has been reported (6). A consumption coagulopathy accompanied by an increased level of fibrin degradation products appeared to play a major role (7). However, these observations were limited to a few patients in the early era of liver transplantation, and comprehensive information is still lacking.

Another difficulty in the intraoperative management of liver transplantation has been actively monitoring the coagulation system and determining the appropriate treatment during dynamic blood volume changes. The use of the thrombelastograph (TEG) was suggested by von Kaulla et al. (4) and Howland et al. (8). However, the efficacy of thrombelastographic monitoring of blood coagulation during liver transplantation has not been established.

The purpose of our study was to investigate the changes in the blood coagulation system, the clinical applicability of thrombelastography as a monitoring system, and the clinical effectiveness of thrombelastography-guided replacement therapy in a large group of patients undergoing liver transplantation.

---

Received from the Departments of Anesthesiology, Medicine, and Surgery, University of Pittsburgh School of Medicine and the Central Blood Bank of Pittsburgh, Pittsburgh, Pennsylvania. Accepted for publication April 4, 1985.

Address correspondence to Dr. Kang, Department of Anesthesiology, Presbyterian University Hospital, De Soto and O'Hara Street, Pittsburgh, PA 15213.

© 1985 by the International Anesthesia Research Society

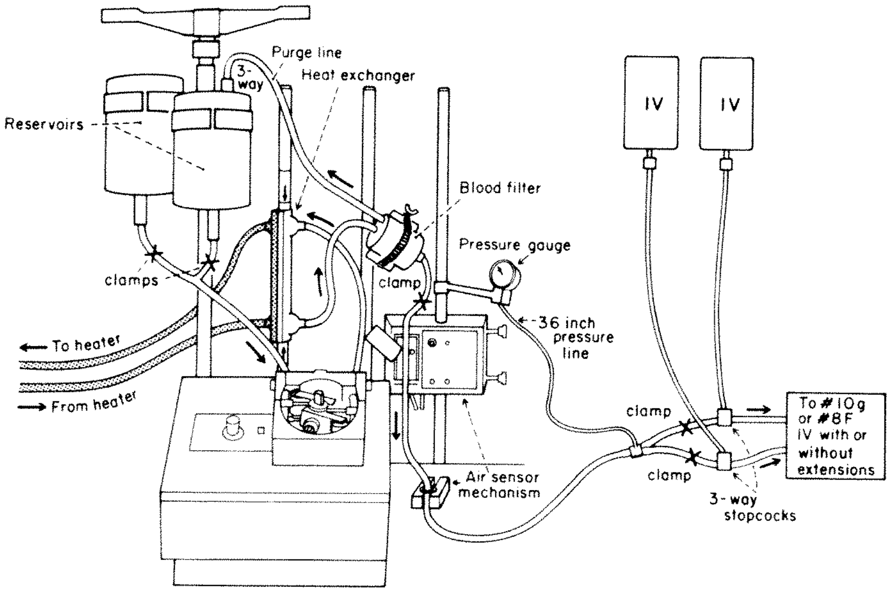


Figure 1. A rapid infusion system, developed by JJ Sassano, MD, of the University of Pittsburgh School of Medicine.

## Methods

Patients undergoing liver transplantation between February 1983 and January 1984 were observed as prospective members for the study. All patients had two indwelling 8.5-French catheters inserted for volume infusion, one in an antecubital vein and another in an internal or an external jugular vein. In addition, a flow-directed pulmonary arterial catheter was inserted via the right internal jugular vein, and an indwelling catheter was placed in a radial artery. Normal saline solution without heparin was used for continuous flushing of the pressure-monitoring catheters to avoid anticoagulant effects. A rapid infusion system was developed (by JJ Sassano, University of Pittsburgh School of Medicine), which was able to deliver warmed, premixed fluid at a rate of up to 2000 ml/min (Fig. 1). This device was used to replace lost blood volume with a fluid composed of red blood cells (RBC), fresh frozen plasma (FFP), and electrolyte solution (Plasma-lyte A, Travenol Laboratories Inc., Deerfield, IL 60015) in a ratio of 300:200:250 ml. All blood products were preserved with citrate phosphate and dextrose with adenine (CPDA-1). Intraoperative volume infusion was guided by systolic blood pressure, heart rate, and pulmonary capillary occlusion pressure measurements. Arterial blood gas tensions and serum electrolytes, glucose, and ionized calcium levels were monitored every hour, though more frequently if clinically indicated.

Coagulation tests employed previously described methods (9–11) and were performed for patient care purposes at times when sudden or profound changes were anticipated. Blood samples (15 ml each) were obtained at various intervals: before induction of anesthesia; 30 min after beginning the operation; thereafter every 2 hr or after infusion of every 6 L of blood volume; 5 min into the anhepatic stage; 30 min into the anhepatic stage; 5 min after reperfusion of the homograft; 30 min after reperfusion; and thereafter every 2 hr or after infusion of every 6 L of blood volume. The blood coagulation profile included measurements of PT; aPTT; thrombin time (TT); reptilase time; levels of factors I, II, V, VII, VIII, IX, X, XI, and XII; fibrin degradation product (FDP) level; euglobulin lysis time (ELT); and platelet count.

At the same time, whole blood was used for thrombelastographic monitoring of blood coagulation (12). Whole blood (0.36 ml) was placed in the Thrombelastograph D (Hellige Company, Freiburg, Germany), and four drops of mineral oil were spread over the blood surface to prevent evaporation of blood. The recording began 4 min from the blood sampling time. The TEG is shown schematically in Figure 2. It repeatedly measures the shear elasticity of a blood clot from the time when the first fibrin strands are formed to the completion of the clot formation, including fibrinolysis. An oscillating cup contains 0.36 ml of whole blood kept at 37°C. A pin, suspended by a torsion wire, is lowered into the blood specimen in the cup. While the blood remains fluid, the container motion does not influence the pin. Once the clot begins to form, the fibrin strands gradually strengthen their hold on the cup and pin. Therefore, the cup is coupled to the pin; and the shear elasticity of the blood clot, which is transmitted to the pin, is recorded on thermal paper. The TEG records the activity of whole blood coagulation (13), including cellular and humoral ele-

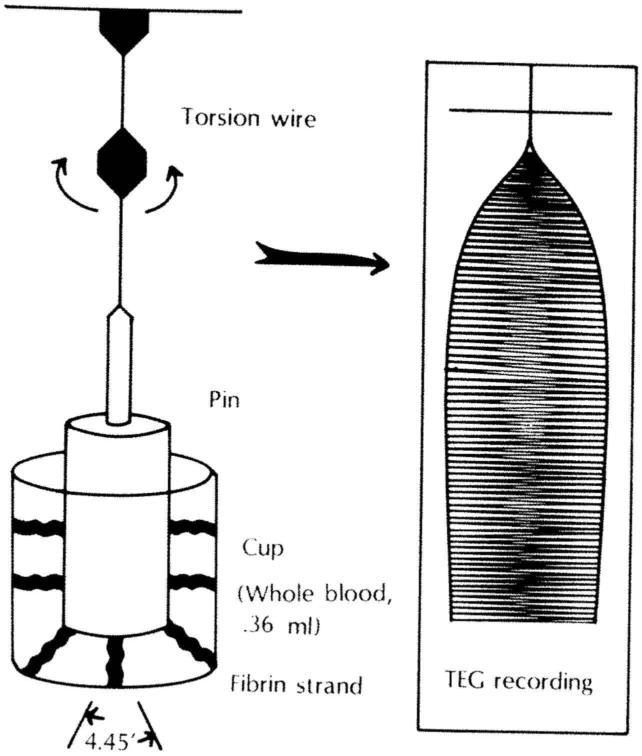


Figure 2. Thrombelastography: sensitive bedside monitoring of coagulation. It measures the shear elasticity of a blood clot from the time when the first fibrin strands are formed to the completion of the clot formation, including fibrinolysis.

ments such as interactions of RBC, platelets, coagulation factors, and calcium. The following variables were measured (Fig. 3): reaction time (*R*, min); maximum amplitude (*MA*, mm); amplitude 60 min after *MA* ($A_{60}$, mm); coagulation time ($R + k$, min); clot formation rate ($\alpha$, °); blood clot lysis time (*F*, min); and blood clot lysis index ($A_{60}/MA \times 100$, %).

The blood product replacement therapy was guided by the results of thrombelastographic monitoring. A prolonged reaction time ($R > 15$ min) was treated with 2 units of FFP and a decrease in maximum amplitude ($MA < 40$ mm), with 10 units of platelets. Cryoprecipitate (6 units) was infused when the above therapy did not improve coagulation or when the clot formation rate was slow ($\alpha < 45°$). However, because the anhepatic stage of surgery included veno–venous bypass (femoral and portal vein to axillary vein) without systemic heparinization, infusion of platelets and cyroprecipitate was withheld during that stage to lessen the chance of thromboembolism. To evaluate the clinical effectiveness of TEG-guided replacement therapy, the blood volume infused in these patients (TEG-monitored group) was compared with that of a group of patients who received liver transplants between August 1981 and January 1983 without TEG monitoring (nonmonitored group).

The measurements of all the coagulation factor levels, thrombelastographic variables, and infused blood product volumes were analyzed by analysis of variance of repeated measures, nonparametric Wilcoxon test, linear regression, and $\chi^2$-analysis. $P < 0.05$ was considered statistically significant.

## Results

Sixty-six adult patients received liver transplants between February 1983 and January 1984. Three patients for whom data were insufficient were excluded from the analysis. The surgical procedure was arbitrarily divided into three distinct stages: stage I, isolation of the host liver; stage II, the anhepatic stage; and stage III, postreperfusion of the graft liver.

### *Changes in Coagulation Profile*

Patients were divided into six groups according to the etiology of their underlying disease: primary biliary cirrhosis, postnecrotic cirrhosis, sclerosing cholangitis, neoplasm, miscellaneous liver diseases, and retransplantation. Preoperative diagnoses in the miscellaneous group were cryptogenic cirrhosis, acute chemical hepatitis, Wilson's disease, hemochromatosis, and $\alpha$1-antitrypsin deficiency. Preoperative coagulation profiles were abnormal in a large proportion of patients: PT in 41 (65%), aPTT in 45 (71%), factor I level in 9 (14%), factor V level in 37 (59%), factor VII level in 35 (56%), factor VIII level in 2 (3%), and platelet count in 44 (70%). ELT was less than 2 hr in 17 patients (27%), and FDP was positive in 15 patients (24%). The mean preoperative coagulation profile of each disease group is shown in Table 1. PT was prolonged in patients of all groups, and it was remarkably prolonged in patients in the postnecrotic cirrhosis and miscellaneous disease groups. aPTT was prolonged in all patients except those with neoplasms. The platelet count was significantly decreased in patients with sclerosing cholangitis and in the miscellaneous disease group. All patients except those in the miscellaneous group demonstrated a relatively normal fibrinogen level. The level of factor V was higher than 0.5 U/ml in the patients of the neoplasm, primary biliary cirrhosis, and retransplantation groups. Factor VIII level was higher than 1.0 U/ml in all but six patients.

Intraoperative coagulation profile and thrombelastographic measurements of patients with primary biliary cirrhosis (11 patients) are shown in Table 2. During stage I of surgery, PT and aPTT remained prolonged. All the coagulation factor levels, including

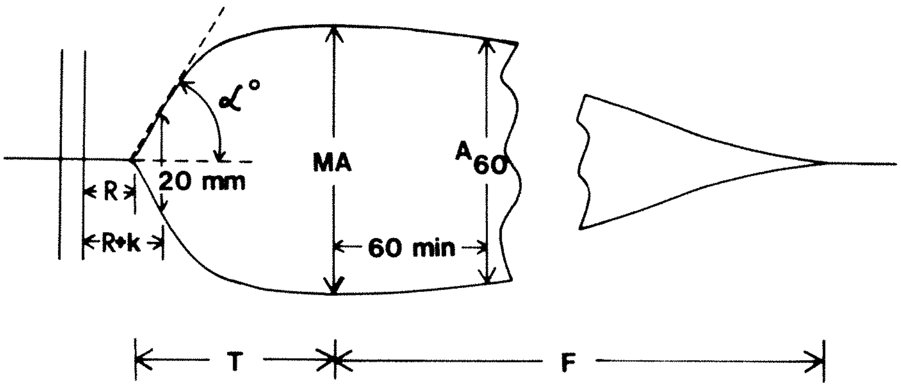


Figure 3. Variables and normal values measured by thrombelastography. Abbreviations: *R*—reaction time, 6–8 min; *R* + *k*—coagulation time, 10–12 min; α—clot formation rate, > 50°; *MA*—maximum amplitude, 50–70 mm; $A_{60}$—amplitude 60 min after *MA*; $A_{60}/MA \cdot 100$—whole blood clot lysis index, > 85%; and *F*—whole blood clot lysis time, > 300 min.

the platelet count, decreased progressively during surgery. In stage II (anhepatic stage) the levels of all coagulation factors did not change significantly, although aPTT was progressively prolonged and ELT became shortened. On reperfusion of the homograft (stage III + 5 min), PT and aPTT were remarkably prolonged, and levels of all other coagulation factors were significantly decreased. With the progress of surgery, coagulation profiles improved slowly, beginning 30 min after reperfusion (III + 30 min). At the end of surgery, PT and aPTT returned toward preoperative values, and platelet counts and the levels of coagulation factors, except factor V, returned toward clinically acceptable levels. The level of factor V, 0.23 ± 0.13 U/ml, was the lowest of the coagulation factors at the conclusion of surgery. Reptilase time and TT were measured in all 11 patients; both were moderately prolonged in all these patients, indicating a possible dysfibrinogenemia. A remarkably prolonged TT was noted in three patients: two at stage II and one at the beginning of stage III. A significant change was seen in ELT. The mean ELT, 215 ± 77 min at the time of induction of anesthesia, decreased progressively during the first stage of surgery. It reached a minimum value at the time of reperfusion of the homograft (68 ± 53 min) and had returned toward the preoperative value at 2 hr in stage III (III + 120 min).

Intraoperative change in fibrinolytic activity in all patients is shown in Table 3. Four patients had an ELT of less than 1 hr at the beginning of surgery; that number increased to 21 by the time of homograft reperfusion. ELT improved toward preoperative values at the end of surgery, remaining shorter than 1 hr in only one patient. A significant number of patients (15) had a slightly positive test for FDP at the beginning of surgery. The number increased to 26 patients by 2 hr after reperfusion of the homograft, and FDP remained positive in 22 patients at the conclusion of surgery, although the concentrations of FDP were never high.

### *Thrombelastographic Variables*

The intraoperative change in TEG variables of patients with primary biliary cirrhosis is shown in Table 2. Preoperative values indicated a slightly prolonged reaction time (*R*). The maximum amplitude (*MA*) and clot formation rate (α) were 54.6 ± 11.2 mm and 55.5 ± 8.5°, respectively. The whole blood clot lysis index ($A_{60}/MA \times 100$) was 83%, which indicates whole blood clot lysis activity. The *R* value was prolonged during the early phase of the third stage of surgery. It was prolonged significantly at the time of reperfusion of the homograft (11.2 ± 5 min) and returned toward its preoperative value at 2 hr in stage III (8.8 ± 3.0 min). The changes in *R* + *k* were similar to those in *R*. The whole blood clot lysis index decreased progressively from the beginning of surgery, and the lowest value was observed in the middle of the anhepatic stage. It improved after reperfusion of the homograft and returned toward the preoperative value at 2 hr in stage III. Intraoperative change of whole blood clot lysis activity in all patients is shown in Table 3. Blood from three patients lysed within 2 hr at induction of anesthesia; whole blood clot lysis was seen most frequently from the middle of stage II to 30 min into stage III. No patient's blood lysed within 2 hr at the conclusion of surgery.

### *Correlation of Thrombelastographic Variables and Coagulation Profile*

To determine the correlation between the conventional coagulation profile and the TEG variables, preoperative values were compared by linear regression analysis. In general, correlation between the variables of TEG and those of the coagulation profile was poor.

Table 1. Preoperative Coagulation Profile of Liver Transplantation Patients

| Variables | Normal range | Neoplasm | Primary biliary cirrhosis | Postnecrotic cirrhosis | Sclerosing cholangitis | Miscellaneous Disease | Retransplant | All patients |
|---|---|---|---|---|---|---|---|---|
| Number of patients | | 9 | 13 | 11 | 6 | 9 | 15 | 63 |
| PT (sec) | 10.8–13.0 | 13.3 ± 4.0 | 13.9 ± 1.7 | 15.7 ± 1.4 | 13.3 ± 3.6 | 18.9 ± 5.4 | 13.2 ± 1.5 | 14.8 ± 3.7 |
| aPTT (sec) | 26–34 | 34.1 ± 6.3 | 41.0 ± 8.7 | 40.2 ± 4.1 | 42.4 ± 10.1 | 46.7 ± 10.6 | 41.7 ± 14.2 | 41.5 ± 13.9 |
| Platelets (1000/mm$^3$) | 150–450 | 245 ± 151 | 181 ± 199 | 162 ± 178 | 86 ± 19 | 82 ± 64 | 116 ± 115 | 147 ± 144 |
| Fibrinogen (mg %) | 150–450 | 323 ± 166 | 382 ± 116 | 247 ± 134 | 238 ± 44 | 167 ± 86 | 301 ± 149 | 292 ± 138 |
| Factor V (U/ml) | 0.5–1.5 | 0.82 ± 0.41 | 0.54 ± 0.27 | 0.35 ± 0.12 | 0.47 ± 0.20 | 0.28 ± 0.23 | 0.66 ± 0.29 | 0.53 ± 0.32 |
| Factor VII (U/ml) | 0.5–1.5 | 0.56 ± 0.25 | 0.83 ± 0.35 | 0.35 ± 0.25 | 0.71 ± 0.49 | 0.28 ± 0.24 | 0.53 ± 0.26 | 0.57 ± 0.39 |
| Factor VIII (U/ml) | 0.5–1.5 | 1.42 ± 0.33 | 2.03 ± 0.73 | 1.82 ± 0.93 | 2.53 ± 1.30 | 2.30 ± 0.70 | 1.92 ± 1.35 | 2.00 ± 0.90 |
| ELT (min) | >300 | 218 ± 48 | 215 ± 77 | 163 ± 87 | 218 ± 67 | 132 ± 68 | 247 ± 86 | 202 ± 81 |

Sixty-three patients, values are mean ± SD.

Table 2. Intraoperative Changes in Coagulation of Patients with Primary Biliary Cirrhosis

| | | Stage I | Stage II | | Stage III | | | |
|---|---|---|---|---|---|---|---|---|
| | Before operation | 120 min | 5 min | 30 min | 5 min | 30 min | 120 min | End |
| PT (sec) | 13.9 ± 1.7 | 13.7 ± 1.0 | 14.0 ± 1.3 | 13.8 ± 1.2 | 15.4 ± 1.6[a] | 15.7 ± 1.5[a] | 15.0 ± 1.4 | 14.6 ± 1.4 |
| aPTT (sec) | 41.0 ± 8.7 | 40.2 ± 7.7 | 46.0 ± 12.9 | 51.2 ± 16.0 | 75.2 ± 39.2[a] | 61.5 ± 23.6[a] | 46.0 ± 9.7 | 38.4 ± 3.8 |
| Platelets (1000/mm$^3$) | 181 ± 199 | 150 ± 122 | 149 ± 120 | 154 ± 122 | 124 ± 63[a] | 132 ± 61 | 134 ± 82 | 143 ± 74 |
| Fibrinogen (mg %) | 323 ± 166 | 288 ± 100 | 252 ± 113 | 235 ± 88 | 194 ± 93[a] | 195 ± 101[a] | 191 ± 90[a] | 210 ± 92 |
| Factor V (U/ml) | 0.54 ± 0.27 | 0.43 ± 0.22 | 0.35 ± 0.19 | 0.38 ± 0.19 | 0.26 ± 0.18[a] | 0.22 ± 0.13[a] | 0.21 ± 0.11[a] | 0.23 ± 0.13[a] |
| Factor VII (U/ml) | 0.83 ± 0.35 | 0.71 ± 0.37 | 0.62 ± 0.31 | 0.65 ± 0.27 | 0.52 ± 0.23[a] | 0.52 ± 0.18[a] | 0.53 ± 0.18 | 0.51 ± 0.17 |
| Factor VIII (U/ml) | 2.03 ± 0.73 | 1.81 ± 0.86 | 1.51 ± 0.88 | 1.49 ± 0.75 | 1.11 ± 0.70[a] | 0.82 ± 0.53[a] | 0.87 ± 0.44[a] | 0.93 ± 0.35[a] |
| ELT (min) | 215 ± 77 | 134 ± 93 | 140 ± 88 | 101 ± 77[a] | 68 ± 53[a] | 108 ± 45 | 155 ± 63 | 185 ± 70 |
| $R$ (min) | 8.5 ± 2.4 | 8.2 ± 3.6 | 6.6 ± 3.4 | 7.5 ± 2.3 | 11.2 ± 5.0[a] | 9.7 ± 2.7 | 8.8 ± 3.0 | 8.0 ± 2.9 |
| $R + k$ (min) | 12.0 ± 2.7 | 12.0 ± 6.3 | 9.5 ± 2.5 | 11.0 ± 2.2 | 23.5 ± 16.4[a] | 15.0 ± 6.1 | 12.5 ± 4.5 | 10.0 ± 2.6 |
| $\alpha$ (°) | 55.5 ± 8.5 | 53.8 ± 12.2 | 53.6 ± 10.4 | 53.1 ± 7.4 | 39.1 ± 17.5[a] | 48.6 ± 10.5 | 50.6 ± 12.0 | 55.1 ± 8.0 |
| $MA$ (mm) | 54.6 ± 11.2 | 57.3 ± 9.4 | 52.3 ± 11.0 | 51.3 ± 9.4 | 38.2 ± 14.5[a] | 51.7 ± 8.9 | 51.5 ± 11.9 | 52.1 ± 10.8 |
| $A_{60}/MA\cdot100$ (%) | 83.0 ± 7.8 | 76.4 ± 14.5 | 73.9 ± 27.0 | 65.5 ± 35.5 | 75.8 ± 34.4 | 79.8 ± 29.3 | 92.2 ± 8.6[a] | 91.7 ± 6.7[a] |

Eleven patients; values are mean ± SD. [a]Significantly different from the corresponding preoperative value ($P < 0.05$).

However, the reaction time correlated best with aPTT ($r = 0.49$, $P < 0.001$). $MA$ correlated better with platelet count ($r = 0.59$, $P < 0.001$) and fibrinogen level ($r = 0.64$, $P < 0.001$). The whole blood clot lysis time ($F$) did correlate with ELT ($r = 0.54$, $P < 0.05$). There were 45 occasions when patients received platelets alone. The mean increase in platelet count was 40,200 ± 31,400/mm$^3$ after infusion of 10 units of platelets; it correlated best with the $MA$ value, which increased 13.2 mm. When 6 units of cryoprecipitate were given alone, factor I increased by 37 mg% and factor VIII by 13 U/ml, while aPTT decreased by 5.7 sec. The corresponding changes in TEG variables were a decrease in reaction time by 1.2 min and an increase in clot formation rate by 9.4°.

### *Comparison of Thrombelastograph-Monitored and Nonmonitored Groups*

The blood volume infused to patients in our series was compared with that required by a group of patients who received liver transplants between March 1981 and January 1983, and who were not monitored by TEG. Five patients in the monitored group who received more than 100 units of RBC transfusion were excluded from the analysis. Seventeen patients in the nonmonitored group were excluded from the comparison—five patients who required more than 100 units of RBC and 12 patients who underwent veno–venous bypass with systemic heparinization, some of whom developed uncontrollable bleeding. The preoperative diagnoses of patients in the two groups were not different ($P > 0.5$). The volume of blood given to patients in the two groups is shown in Table 4. Patients in the TEG-monitored group received 17 ± 12.9 units of RBC, whereas patients in the nonmonitored group required 26.7 ± 23.8 units of RBC ($P < 0.05$). A significant reduction in FFP infusion (18.3 ± 12.5 vs 26.7 ± 24.1 units) and a decrease in total fluids infused (20.2 ± 11.2 vs 31.4 ± 19.2 L) were noted in patients of the TEG-monitored group. On the other hand, significantly

Table 3. Intraoperative Changes in Number of Patients with Fibrinolytic Activity

| | | Stage I | | Stage II | | Stage III | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Before operation | 30 min | 120 min | 5 min | 30 min | 5 min | 30 min | 120 min | End |
| ELT | | | | | | | | | |
| >1 hr | 48 | 41 | 25 | 35 | 29 | 27 | 21 | 37 | 43 |
| <1 hr | 4 | 10 | 15 | 14 | 20 | 21 | 13 | 1 | 1 |
| FDP | | | | | | | | | |
| Negative | 36 | 37 | 36 | 37 | 31 | 34 | 30 | 27 | 31 |
| Positive | 15 | 16 | 16 | 17 | 21 | 20 | 22 | 26 | 22 |
| *F* | | | | | | | | | |
| >2 hr | 55 | 53 | 51 | 52 | 49 | 49 | 46 | 55 | 58 |
| <2 hr | 3 | 5 | 7 | 6 | 10 | 10 | 12 | 3 | 0 |

more platelets (20.8 ± 12.8 vs 14.1 ± 13.7 units) and cryoprecipitate (17.2 ± 8.5 vs 10.2 ± 4.5 units) were infused to the TEG-monitored patients. The number of donors from whom each patient received blood was similar between the two groups (67.9 ± 43.9 vs 71.4 ± 63.4).

## Discussion

As might be expected of patients with end-stage liver disease, preoperative coagulation profiles of many subjects studied showed prolonged PT and aPTT and decreased levels of factors produced by the liver. Coagulopathy was worse preoperatively in patients with miscellaneous types of liver disease and with postnecrotic cirrhosis because these patients have more parenchymal hepatocellular damage, which disrupts the synthesis of the blood coagulation factors. Other patients, such as those with neoplasms, may have close to normal hepatic function. Supranormal levels of fibrinogen and factor VIII activity were observed in many of our patients. A similar high level of factor VIII was found previously (14) and may result from increased production related to a stress response, release from damaged liver cells, or impaired catabolism of factor VIII (15). Preoperative fibrinogen level was lower than normal in only 20% of the patients. However, moderate prolongation of both TT and reptilase time was common and suggests a possible dysfibrinogenemia. Abnormal fibrin polymerization is known to occur in liver disease (16) and is reported to be related to an excessive sialic acid content in the fibrinogen molecule (17,18). The clinical significance of the acquired dysfibrinogenemia in patients with liver disease and its role in patients undergoing liver transplantation requires further investigation.

Throughout the surgical procedure, a fluid composed of RBC, FFP, and Plasma-lyte A in a ratio of 300:200:250 ml was used for volume replacement. RBC was mixed with FFP to supplement coagulation factors. Plasma-lyte A was added to decrease the loss of RBC and possibly to improve the circulatory rheology. Plasma-lyte A was chosen because it does not contain calcium, which can initiate clotting in the rapid infusion system; it does not contain glucose, which may cause hyperglycemia during massive blood transfusion; and it is isoosmolar. The blood mixture had levels of hematocrit, 27 ± 2; hemoglobin, 9 ± 1.2 mg%; factor I, 130 mg%; factor II, 0.59 U/ml; factor V, 0.21 U/ml; factor VII, 0.58 U/ml; and factor VIII, 0.57 U/ml. Once blood volume was replaced by this mixture, platelets, fibrinogen, and factor VIII were replenished with transfusion of platelets or cryoprecipitate, guided by TEG monitoring. A coagulation factors-rich blood mixture was transfused, and the plasma levels of coagulation factors reached the levels in the transfused blood mixture rapidly as surgery progressed. The change is more likely due to a dilutional effect associated with surgical bleeding. As long as blood was simply entering the patient by transfusion and leaving by exsanguination, the dilutional effects should not bring the coagulation factors below those in the infused blood mixture. If fibrinolysis or intravascular coagulation occurred, differential falls in certain factors might be seen.

No attempt was made to correct coagulopathy during unheparinized veno–venous bypass in the anhepatic stage, in order to minimize possible thrombosis or embolization. Only RBC and FFP were infused to replace the blood volume. The increase in fibrinolytic activity was the most significant change in the coagulation pattern during the anhepatic stage. This relative lack of change in coagulation profile measurements may be due to the relatively short duration of the second stage (89 ± 21 min; compared with 221 ± 80 min, stage I; and 343 ± 123 min, stage III) or to the use of veno–venous bypass (19). It appears that the veno–venous bypass system, which used a heparin-coated Gott Aneurysm Shunt (Sherwood Medical, St. Louis, MO), did not interfere with the

Table 4. Comparison of Transfused Blood Volume between Thrombelastograph-Monitored Patients and Nonmonitored Patients

| Blood products | TEG-monitored patients ($n$ = 58) | Nonmonitored patients ($n$ = 47) |
|---|---|---|
| Red blood cells (unit) | 17.0 ± 12.9[a] | 26.7 ± 23.8 |
| Fresh frozen plasma (unit) | 18.3 ± 12.5[a] | 26.7 ± 24.1 |
| Platelets (unit) | 20.8 ± 12.8[a] | 14.1 ± 13.7 |
| Cryoprecipitate (unit) | 12.2 ± 14.2[a] | 3.9 ± 12.9 |
| Total blood products (unit) | 67.9 ± 43.9 | 71.4 ± 63.4 |
| Crystalloid (litre) | 10.2 ± 4.5[a] | 17.2 ± 8.5 |
| Total volume infused (litre) | 20.2 ± 11.2[a] | 31.4 ± 19.2 |

Values are mean ± SD. [a]Significantly different from the corresponding values of the nonmonitored patients ($P < 0.05$).

coagulation system, by thrombosis or by coagulopathy, and may even have played a beneficial role. By decompressing the portal venous system and maintaining venous return from the lower extremities, it could have decreased venous pressure to decrease bleeding and reduced the congestive ischemia of the viscera, which in turn might have minimized the metabolic acidosis that could have adversely affected the blood coagulation system.

Reperfusion of the homograft was associated with significant coagulopathy, which was clearly demonstrated by the TEG measurements: prolonged *R*, prolonged *R* + *k*, decreased *MA*, decreased *α*, and decreased *F* (which was shortened to 92 min, reflecting the decreased function of coagulation factors, including fibrinogen and platelets, and active whole blood lysis). These findings, in agreement with reports by Groth (6) and by von Kaulla et al. (4), might have resulted from pathophysiologic changes that occur on reperfusion of the graft liver. First, there is an exaggerated dilutional effect. The influx of the organ preservation solution from the donor liver may contribute further to the dilution of coagulation factors. Second, an active fibrinolytic process is evident in many patients. This could be due to release of tissue plasminogen activator from vascular endothelium (20) or to activation of protein C (21). Third, other investigators stressed disseminated intravascular coagulation (DIC) as a major cause of the change (2,5), but there is little evidence of DIC in this study. Groth et al. suggested that loss of hepatic clearance function played a role in fibrinolytic activation or that antigen–antibody reaction might lead to DIC (2). However, the lack of high levels of circulating fibrin monomers and FDP found in this study does not support a major role for DIC as a cause of excessive bleeding. In addition, an attempt to identify microthrombi in major organs of a canine liver transplant recipient after clinical evidence of intravascular coagulation was not successful (22). No clinical sign of ischemic injury caused by microthrombi in major vital organs was seen in our patients. Fourth, the possibility of trapping of coagulation factors and platelets, especially by the poorly preserved donor liver, can be considered. However, the mean increase in platelet count after platelet infusion during the early part of the third stage of surgery was not different from that in the first stage. Fifth, as postulated by Stremple et al., levels of heparin or a heparin-like substance may be increased (23). However, of 13 patients who received the TT and reptilase time test, TT was prolonged significantly in only two patients, indicating that heparin or a heparin-like substance plays a rather minor role in coagulopathy. Finally, the effects of other humoral and metabolic factors should be emphasized. Metabolic acidosis, decrease in cardiovascular performance, decreased plasma ionized calcium level, decrease in body temperature, and hyperkalemia were observed during reperfusion in most patients; and all of these could adversely affect the coagulation system. The blood coagulability measured by TEG improved without significant changes in levels of coagulation factors 30 min after reperfusion in a significant number of patients. That is not sufficient time to expect the functional recovery of the donor liver, although it coincided with the recovery of the above physiologic variables. Thus metabolic and humoral changes that occur with the reperfusion of the homograft may interfere with the hemostatic process more than has been recognized.

All coagulation profile and TEG variables started to improve 30 min after reperfusion of the liver and, with the exception of factor V and factor VIII, all the factor levels and ELT returned toward the baseline value within 2 hr after reperfusion. This agrees with the findings of Groth (6), and it appears that recovery of the coagulation system coincides with bile production and the metabolism of citrate (Marquez JM, unpublished data, 1984).

In this series of patients, blood replacement therapy was guided by TEG monitoring. TEG, developed in the 1950s, has been used mostly for research purposes and is a simple, reliable, and sensitive method. A general assessment of blood coagulation status can be obtained within 30 min (8,24), and the coagulation process is assessed continuously and rapidly in the operating room. TEG measures the coagulation process in whole blood, rather than testing blood coagulability in anticoagulated plasma, as is commonly done to obtain the conventional analytic coagulation profile. The interpretation of TEG and its relation to the conventional coagulation profile has been established by several researchers (25,26). The reaction time (*R*) is closely related to aPTT. The maximum amplitude (*MA*) is a reflection of platelet function and activity of factor XIII. The rate of clot formation ($\alpha$) primarily reflects the function of fibrinogen, and it increases with improved platelet function. The whole blood clot lysis time (*F*) is reported to be closely related to ELT. To express the activity of whole blood clot lysis, the ratio $A_{60}:MA$ was used.

In general, the correlation between the TEG variables and coagulation profile measurements in the patients studied is similar to results published by others, although it was not high in these patients, probably because of both the large standard deviations in the individual data and other physiologic changes. Since replacement of blood products was guided by the TEG monitoring, as described in Methods, there were fewer significant changes in *R*, $R+k$, *MA*, and $\alpha$ values during the first stage, although there were decreases in coagulation factors and platelets. This discrepancy may indicate that blood coagulability was maintained in spite of low but higher than critical levels of coagulation factors.

The effectiveness of the TEG-guided replacement therapy is shown in a representative TEG pattern (Fig. 4). Poor preoperative coagulation status was improved by selective transfusion of FFP, platelets, and cryoprecipitate; and blood coagulability was normal at the end of surgery after transfusion of 46 units of RBC, 48 units of FFP, 20 units of platelets, and 12 units of cryoprecipitate. The clinical significance of TEG-guided replacement therapy is demonstrated in the volumes patients received during the surgical procedure. Treatment of patients in the control group, who received liver transplants from 1981 to 1982, was guided by clinical impression and the results of PT, aPTT, and platelet count. Since TEG monitoring began, the required volume of fluid infusion has decreased by 33%. Defects in the coagulation system were treated with platelets or cryoprecipitate when needed. All but two patients in the TEG-monitored group received veno–venous bypass, and the improved surgical technique could have contributed to the reduction in blood loss. However, because of the magnitude of the intraoperative bleeding, a controlled, randomized study could not be justified. Furthermore, it is not unreasonable to speculate that patients in the TEG-monitored group had better blood coagulability because TEG patterns were normal toward the end of surgery. The total number of blood donors to which patients were exposed remained similar, even though patients in the TEG-monitored group received more platelets and cryoprecipitate; therefore exposure to hepatitis or acquired immune deficiency syndrome was not increased in patients of the TEG-monitored group.

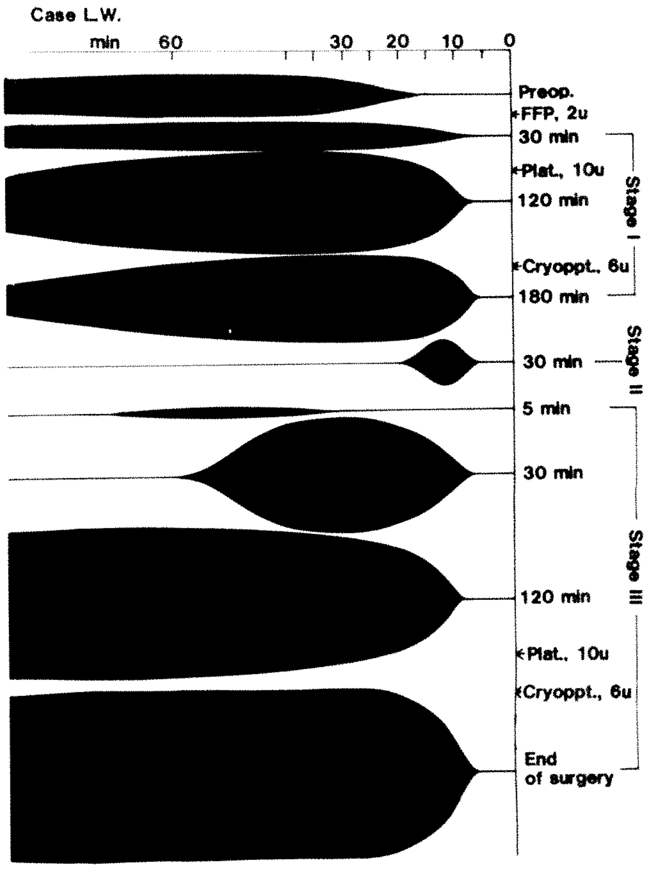


Figure 4. Thrombelastographic pattern of one patient. Reaction time, maximum amplitude, and clot formation rate improved after sequential transfusion of FFP, platelets, and cryoprecipitate. Rapid whole blood clot lysis was demonstrated during the second stage and the early part of the third stage of surgery. Transfusion of platelets and cryoprecipitate normalized the TEG pattern at the end of the operation. This patient was transfused 46 units of RBC, 48 units of FFP, 20 units of platelets, and 12 units of cryoprecipitate.

In this series of 66 patients, very severe coagulopathy was observed ranging from no clotting at all to a rapid whole blood clot lysis (within 0.5 hr), which often was associated with blood transfusions in excess of 50 L. Normalizing the levels of platelets and coagulation factors may not always be possible. However, maintaining the blood coagulability is critically important for these patients who have marginal or no liver function. This study showed intraoperative changes in coagulation and the clinical effectiveness of TEG monitoring and TEG-guided replacement therapy. Further investigation is required for a better understanding of the clinical use of TEG and antifibrinolytic therapy to reduce morbidity and mortality in patients undergoing liver transplantation.

The authors thank Mr. Jeffrey M. Yoffe and Mr. Mark Zapp for their technical assistance, Ms. Lisa Cohn for her editorial help, Dr. Ray McKenzie for his support, and the Hellige Company of Germany for the loan of equipment.

## References

1. Starzl TE, Iwatsuki S, Van Thiel DH, et al. Evolution of liver transplantation. Hepatology 1982;2:614–36.
2. Groth CG, Pechet L, Starzl TE. Coagulation during and after orthotopic transplantation of the human liver. Arch Surg 1969;98:31–4.
3. Toghill PJ, Green S, Ferguson R. Platelet dynamics in chronic liver disease with special reference to the role of spleen. J Clin Pathol 1977;30:367–71.
4. von Kaulla KN, Kaye H, von Kaulla E, Marchioro TL, Starzl TE. Changes in blood coagulation, before and after hepatectomy or transplantation in dogs and man. Arch Surg 1966;92:71–9.
5. Flute PT, Rake MO, Williams R, Seaman MJ, Calne RY. Liver transplantation in man—IV, haemorrhage and thrombosis. Br Med J 1969;3:20–3.
6. Groth CG. Changes in coagulation. In: Starzl TE, ed. Experience in hepatic transplantation. Philadelphia: WB Saunders, 1969;159–75.
7. Pechet L, Groth CG, Daloze PM. Changes in coagulation and fibrinolysis after orthotopic canine liver transplantation. J Lab Clin Med 1969;73:91–102.
8. Howland WS, Castro EB, Fortner JB, Gould P. Hypercoagulability–thrombelastographic monitoring during extensive hepatic surgery. Arch Surg 1974;108:605–8.
9. Lewis JH. Coagulation defects. JAMA 1961;178:1014.
10. Lewis JH. Hemostasis and hemorrhage. Sci Clin 1971;1:1–66.
11. Lewis JH, Spero JA, Hasiba U. Diagnostic methods: laboratory tests. In: Bleeding disorders. Garden City, NY: Medical Exam Publishing Co, Inc, 1978:22–34.
12. De Nicola P. Thrombelastography. Springfield, IL: Charles C Thomas, 1957.
13. Raviv G, Cramon DB, Epstein M, Zuckerman L, Caprini JA. Electronic readout for three-channel thrombelastograph. J Med 1978;9:17–31.
14. Bontempo FA, Lewis JH, Van Thiel DH, et al. The relation of preoperative coagulation findings to diagnosis, blood usage and survival in adult liver transplantation. Transplantation (in press).
15. Green AJ, Ratnoff OD. Elevated antihemophilic factor (AHF, factor VIII) procoagulant activity and AHF-like antigen in alcoholic cirrhosis of the liver. J Lab Clin Med 1974;83:189–97.
16. Ragni MV, Lewis JH, Spero JA, et al. Bleeding and coagulation abnormalities in alcoholic cirrhotic liver disease. Clin Exp Res 1982;6:267–74.
17. Fletcher AP, Biederman O, Moore D, Alkjaersig N, Sherry S. Abnormal plasminogen–plasmin system activity (fibrinolysis) in patients with hepatic cirrhosis: its cause and consequences. J Clin Invest 1964;43:681–95.
18. Martinez J, Palascak JE, Kwasniak D. Abnormal sialic acid content of the dysfibrinogenemia associated with liver disease. J Clin Invest 1978;61:535–8.
19. Shaw BW, Martin MJ, Marquez JM, et al. Venous bypass in clinical liver transplantation. Ann Surg 1984;200:524–34.
20. Collen D. On the regulation and control of fibrinolysis. Thromb Haemostas 1980;43:77.
21. Esmon C, Owen W. Identification of an endothelial cell cofactor for thrombin-catalyzed activation of protein C. Proc Natl Acad Sci USA 1981;78:2249.
22. Hutchinson DE, Genton E, Porter KA, et al. Platelet changes following clinical and experimental hepatic homotransplantation. Arch Surg 1968;97:27–33.
23. Stremple JF, Hussey CV, Ellison EH. Study of clotting factors in liver homotransplantation. Am J Surg 1966;111:862–9.
24. Kang YG, Abouleish E. Thrombelastography in obstetrics (Abstract). Anesthesiology 1981;55(suppl):A304.
25. Zuckerman L, Cohen E, Vagher JP, Woodward E, Caprini JA. Comparison of thrombelastography with common coagulation tests. Thromb Haemostas 1981;46:752–6.
26. Howland WS, Schwizer O, Gould P. A comparison of intraoperative measurements of coagulation. Anesth Analg 1974;53:657–63.

# Comparison of Morphine, Meperidine, Fentanyl, and Sufentanil in Balanced Anesthesia:

## A Double-Blind Study

Joan W. Flacke, MD, Byron C. Bloor, PhD, Benjamin J. Kripke, MD, Werner E. Flacke, MD, Christine M. Warneck, MD, Aaron P. Van Etten, MS, David H. Wong, MD, and Ronald L. Katz, MD

FLACKE JW, BLOOR BC, KRIPKE BJ, FLACKE WE, WARNECK CM, VAN ETTEN AP, WONG DH, KATZ RL. Comparison of morphine, meperidine, fentanyl, and sufentanil in balanced anesthesia: a double-blind study. Anesth Analg 1985;64:897–910.

*A double-blind study comparing four narcotic analgesics of different potencies, meperidine, morphine, fentanyl, and sufentanil, was performed on consenting patients undergoing general or orthopedic surgery under balanced anesthesia. Blood pressure, measured through an indwelling arterial catheter, was recorded continuously, as were ECG and heart rates. The narcotics, made up in equipotent concentrations, were given as indicated by hemodynamic and clinical signs. Arterial blood samples were taken before and after induction, after intubation, before and after incision, at intervals during the operation, and postoperatively. Hemodynamic values and plasma levels of catecholamines during and after induction, intubation, incision, and throughout the operation were least in patients given sufentanil and greatest in those who received morphine or meperidine. Heart rates increased significantly after induction with meperidine and were significantly higher after intubation in morphine-treated and meperidine-treated patients than they were in patients receiving sufentanil. Intraoperatively, mean arterial blood pressure, rate–pressure product, and plasma norepinephrine levels were lowest in patients receiving sufentanil. Intraoperative plasma epinephrine levels were lowest in patients receiving sufentanil and meperidine. Because of increases in blood pressure, heart rate, or both to greater than 15% above control values, supplementation with a potent inhalational agent was necessary in 38%, 30%, and 29% of the patients given meperidine, morphine, and fentanyl, respectively. No sufentanil patient required supplementation. Side effects, including histamine release accompanied by tachycardia and hypotension, were most frequent and most severe in patients who received meperidine. After extubation, marked increases in heart rate, blood pressure, and plasma norepinephrine and epinephrine occurred in some patients in each group. The incidence of postoperative respiratory depression was greatest in patients given morphine (mean dose of naloxone 8.6 μg/kg) and least with sufentanil (mean dose of naloxone 1.8 μg/kg) and fentanyl (3.2 μg/kg naloxone).*

Key Words: ANESTHESIA, INTRAVENOUS—narcotics. ANALGESICS—morphine, meperidine, fentanyl, sufentanil.

Opioid analgesics do not share the direct cardiovascular depressant effects of volatile inhalational agents (1). Therefore they are widely used, not only as the main anesthetic agents during cardiac surgery, but also in smaller doses during balanced anesthesia for general surgical procedures. Morphine and its derivatives, as well as meperidine, have been utilized successfully for this purpose, as has the more potent agent, fentanyl. Recently, sufentanil, a new opioid 5–10 times more potent than fentanyl (2,3), with the same or a slightly shorter duration of action (4,5), has been investigated clinically. The rationale for the introduction of these more potent opioids is improved selectivity, i.e., fewer molecules are needed to interact with target opiate receptors in the central nervous system. Hence, there is decreased likelihood of nonspecific, nonnarcotic receptor-mediated side effects. Indeed, studies in animals have demonstrated a positive relationship between opioid potency and therapeutic index (6). Moreover, several clinical studies (3,4,7,8), in which investigators used very high doses of potent narcotic analgesics for cardiac surgery, re-

---

Received from the Department of Anesthesiology, University of California Los Angeles, School of Medicine, Los Angeles, California. Accepted for publication April 12, 1985.

Address correspondence to Dr. J. Flacke, Department of Anesthesiology, University of California Los Angeles, School of Medicine, Los Angeles, CA 90024.

© 1985 by the International Anesthesia Research Society

sulted in observations of greater hemodynamic stability and less histamine release than with morphine. Concomitant respiratory depression from these high doses required a period of prolonged postoperative ventilation only slightly shorter than that seen with morphine.

The present investigation was designed to compare the advantages and disadvantages of the older and less potent narcotics, morphine and meperidine, with fentanyl and sufentanil as components of balanced anesthesia for relatively short, noncardiac operations. The purpose was to see whether there are differences among these four agents in ability to provide analgesia and cardiovascular and autonomic stability during surgical stimulation in doses that do not cause prolonged respiratory depression. In addition, the relationship of drug effects to potency was examined, as was the occurrence of side effects such as chest wall rigidity, histamine release, and postoperative nausea and vomiting. To carry out a meaningful, unbiased comparison, we designed a study protocol based upon double-blind conditions, equivalent doses of opioids, rigid and definite guidelines for narcotic administration and reversal, and continuous hemodynamic monitoring.

## Methods

### *Study Design*

Sixty ASA class 1 and 2 patients between the ages of 18 and 65, without history of cardiovascular disease, drug allergy, or narcotic abuse, and scheduled to undergo general or orthopedic surgery, were identified on the day before operation. The study, which had been approved by the UCLA Human Subjects Protection Committee, was explained to them; and their written informed consent was obtained. Patients were then assigned randomly (computer-generated random numbers) to receive one of four agents (sufentanil, fentanyl, morphine, or meperidine) as part of their anesthetic management. After 40 patients had been studied, morphine was dropped from the protocol (see results), and the remaining 20 patients were rerandomized to receive one of the other three drugs.

All patients were premedicated with diazepam, 5–10 mg, and droperidol, 0.5 mg, given either orally or intramuscularly (respectively) on the ward 60 min before coming to the operating room, or given intravenously (both drugs) in the preoperative room, approximately 25 min before induction. After patients arrived in the operating room, intravenous and radial artery catheters were placed with local anesthesia, ECG electrodes were attached, and baseline measurements made. The opiates were supplied in 10-ml syringes labeled only "Narcotic. Equivalent in potency to 33 mg/ml meperidine." (Meperidine was used as the reference drug as it was, at that time, the most commonly used narcotic component of balanced anesthesia in this institution and hence most likely to be familiar to residents and staff.) The syringes contained one of the following: sufentanil, 10 μg/ml; fentanyl, 50 μg/ml; morphine, 4 mg/ml; or meperidine, 33.3 mg/ml. Relative potencies were assigned on the basis of literature reports (2,3,6,9). Although anesthesia was carried out by the anesthesia resident assigned to the patient, one of three of the investigators was the attending anesthesiologist who supervised and was responsible for the conduct of each case. An additional investigator was present to make sure that the study protocol was followed. None of the anesthesiologists, investigators, or patients knew which drug was being given.

### *Induction Protocol*

After precurarization with 1 mg of pancuronium intravenously and 3 min of breathing 100% oxygen by face mask via a semiclosed circle system, the patient received the opiate intravenously in divided doses (of 1–2 ml), up to a maximum amount of 0.15 ml/kg, unless this loading process was limited by cardiovascular or central nervous system effects such as hypotension or unconsciousness, or by truncal rigidity. During administration of the narcotic, the anesthesiologist instructed the patient to breathe, open eyes, and follow other commands, in order to assess the state of consciousness. Respiration was manually assisted if necessary. After narcotic administration was complete, the patient was given 1–4 mg/kg thiopental intravenously, followed by 1 mg/kg succinylcholine, and the trachea was intubated. The induction of anesthesia was rated as good, satisfactory, fair, or poor by the anesthesiologist involved.

### *Maintenance Protocol*

After intubation, anesthesia was maintained with 60–67% nitrous oxide in oxygen, and ventilation was controlled to maintain normal blood–gas tensions. If muscle relaxation was required, additional pancuronium was given as determined by evaluation of neuromuscular block with a peripheral nerve stimulator. When signs of inadequate anesthesia appeared, such as movement, grimacing, sweating, tearing, or whenever the blood pressure or pulse rate increased more than 15% above the preanesthetic value, the patient was given supplementary doses of narcotic, the doses

Table 1. Characteristics of Patient Groups According to Drug Received

| | | | | | Type of operation | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Drug | *n* | Age (yr) | Weight (kg) | Duration of operation (min) | Major ortho (spine, hip) | Intraabdominal | Gynecologic or urologic | Peripheral (minor ortho, plastic, tumor) | Estimated blood loss (ml) |
| Sufentanil | 17 | 43 ± 3 | 66 ± 4 | 134 ± 19 | 5 | 5 | 2 | 5 | 376 ± 77 |
| Fentanyl | 17 | 40 ± 4 | 68 ± 4 | 175 ± 22 | 6 | 7 | 0 | 4 | 831 ± 182 |
| Morphine | 10 | 37 ± 3 | 72 ± 6 | 140 ± 20 | 4 | 4 | 0 | 2 | 1108 ± 351 |
| Meperidine | 16 | 40 ± 4 | 71 ± 3 | 214 ± 28 | 3 | 8 | 2 | 3 | 739 ± 169 |

Mean values ± SEM. There are no statistically significant intergroup differences in mean age or weight. Types of operation are fairly well distributed. Mean operation times were significantly longer with meperidine than with sufentanil ($P < 0.025$) or morphine ($P < 0.05$). Mean blood loss was significantly greater with fentanyl than with sufentanil. The large mean blood loss seen with morphine was not statistically significantly ($P < 0.05$) different from the other three groups.

ranging from 0.01–0.05 ml/kg, at the discretion of the anesthesiologist. If rapid action with a known drug was deemed necessary, 50–100-mg doses of thiopental could be given also. If hemodynamic hyperactivity or signs of inadequate anesthesia could not be controlled despite the above described narcotic supplementation, the patient was considered a narcotic "failout". In these cases, no further opiate was given, a potent inhalation agent (halothane, enflurane, or isoflurane) was added, and no further hemodynamic data or plasma catecholamine levels from that patient were included in the intraoperative study analysis. (However, data from failout patients were included in postextubation values and in the assessment of the recovery period, see below.)

### *Recovery Protocol*

Narcotic supplements were not given within 30 min of the estimated completion of the surgery. At the end of the operation, residual neuromuscular block was reversed with neostigmine (after atropine) until tetanic nerve stimulation at 60 Hz showed a sustained response. Nitrous oxide was then discontinued, 100% oxygen was substituted, and the patient was observed for return of consciousness (ability to follow commands) and for ability to breathe adequately, defined as a spontaneous respiratory rate greater than 12 per min, an inspiratory force greater than $-25$ cm $H_2O$, and maintenance of an arterial $P_{CO_2}$ of less than 50 torr during undisturbed spontaneous respiration. If these criteria were not met, the patient was given naloxone in a dose of 1.5 μg/kg intravenously, repeated at intervals of 2–3 min until the above defined conditions were achieved. Patients were taken to the recovery room and kept there for careful observation for at least 3 hr. Those who had received naloxone were monitored especially for evidence of recurrent respiratory depression. If renarcotization leading to respiratory depression (as defined above) occurred, additional naloxone injections (1.5 μg/kg each dose) were administered. If respiration was insufficient in spite of these injections, the patient was ventilated artificially until recovery was adequate. After the patient had left the recovery room, the anesthesiologist gave his or her opinion in writing as to which drug had been used. Twenty-four to 48 hr after surgery, patients were interviewed by the attending anesthesiologist and asked for their ratings of induction and recovery, and at this time the anesthesiologist's rating of recovery was made also.

### *Monitors and Measurements*

ECG, intraarterial blood pressure, and heart rate were measured and recorded (Hewlett Packard direct writing polygraph) from before induction until discharge from the recovery room. Rate–pressure products (systolic blood pressure times heart rate) were calculated as an index of overall cardiovascular activity. Arterial blood samples for the determination of plasma norepinephrine, epinephrine, and histamine were drawn before induction (control), after narcotic administration, after thiopental, 1–2 min after intubation, before and 1–2 min after incision, before and 5 min after narcotic supplements, before and after muscle relaxant reversal and naloxone administration, and 1–2 min after extubation. In addition to cardiovascular changes and sympatho–adrenal activity, patients were observed for evidence of muscle rigidity during induction, cutaneous signs of histamine release, and postemergence nausea or vomiting. If present, these side effects were rated by anesthesiologists and investigators as disturbing or nondisturbing, according to their severity and frequency of occurrence. Plasma catecholamine levels were measured by high-performance liquid chromatography (10) and plasma histamine by a modified radioenzymatic method (11).

Table 2. Preinduction (control) Hemodynamic and Catecholamine Values (mean ± SEM)

| Drug | Blood pressure (torr) Systolic | Diastolic | Mean | Heart rate (beats/min) | Rate–pressure product | Plasma catecholamines (pg/ml) NE | EPI |
|---|---|---|---|---|---|---|---|
| Sufentanil | 129.2 ± 4.2 | 68.8 ± 2.3 | 88.9 ± 2.7 | 77.4 ± 3.5 | 10066 ± 671 | 130.3 ± 16.7 | 50.2 ± 9.2 |
| Fentanyl | 129.6 ± 2.2 | 68.9 ± 2.0 | 89.2 ± 1.9 | 76.8 ± 3.4 | 9916 ± 392 | 185.4 ± 18.2 | 40.6 ± 6.0 |
| Morphine | 124.5 ± 6.8 | 70.5 ± 4.2 | 88.5 ± 4.6 | 78.5 ± 2.7 | 9863 ± 776 | 163.9 ± 34.7 | 23.1 ± 4.0 |
| Meperidine | 128.8 ± 5.6 | 66.8 ± 2.4 | 87.5 ± 3.2 | 74.5 ± 3.1 | 9739 ± 764 | 173.8 ± 15.2 | 79.0 ± 27.8 |

Mean values ± SEM. There are no statistically significant ($P < 0.05$) intergroup differences.

Table 3. Induction Drug Doses, Times, and Ratings in the Different Groups

| Drug | Concentration per ml | Relative potency | Calculated induction dose per kg | Actual induction dose per kg | Number who did not receive full induction dose | Time (min) For narcotic administration | Until intubation | Until incision | % Inductions rated good or satisfactory By anesthesiologists | By patient |
|---|---|---|---|---|---|---|---|---|---|---|
| Sufentanil | 10 μg | 400 | 1.5 μg | 1.28 ± 0.06 μg | 8 (47%) | 6.9 ± 0.5 | 9.3 ± 0.5 | 32.4 ± 2.1 | 100% | 100% |
| Fentanyl | 50 μg | 80 | 7.5 μg | 6.97 ± 0.36 μg | 3 (18%) | 7.4 ± 0.5 | 10.2 ± 0.6 | 40.2 ± 2.7 | 100% | 94% |
| Morphine | 4 mg | 1 | 0.6 mg | 0.59 ± 0.02 mg | 0 | 5.6 ± 0.5 | 10.5 ± 1.5 | 31.5 ± 2.0 | 90% | 90% |
| Meperidine | 33.3 mg | 0.12 | 5.0 mg | 4.34 ± 0.21 mg | 8 (50%) | 7.3 ± 0.5 | 10.2 ± 0.6 | 35.9 ± 2.9 | 56% | 100% |

Mean values ± SEM.

In the statistical treatment of demographic, hemodynamic, and laboratory data, we tested intergroup differences for significance first by comparing data using analysis of variance. When significance was demonstrated, individual group differences were isolated using a weighted $t$-test, in which the critical probability for significance ($P$) was calculated as $P/g$, where $g$ was equal to the number of groups (ie, $g$ = 4 drug groups). For example, to achieve significance at the 5% level, $P$ had to be less than 0.05/4 or 0.0125. Intragroup differences were examined by analysis of variance for repeated measure. Bonferroni's modified $t$-test was used to isolate further the differences when analysis of variance for repeated measure showed significance. Linear regression analysis and correlation coefficients were calculated between log (base 10) catecholamine concentrations and heart rate. Correlation coefficients ($r$) with corresponding $P < 0.05$ were considered significant.

Side-effect data was scored in the following manner: no side effect (SE), 0; nondisturbing SE, 1; and disturbing SE, 2. For each patient, a single total side-effect score was calculated by adding the individual scores for each of the seven side effects studied. Differences among drugs were determined by first applying the Kruskal–Wallis statistic, followed by Mann–Whitney $U$-test. All values are given as means ± SEM.

## Results

Partial findings have been reported previously in abstract and discussion form (12–14). Seventeen patients received sufentanil, 17 received fentanyl, 16 received meperidine, and 10 received morphine. Mean ages, weights, operations, times, and blood loss for the four groups are shown in Table 1. Control hemodynamic and catecholamine values are seen in Table 2. Except as noted, there were no significant intergroup differences.

### *Induction of Anesthesia*

Calculated and actual induction drug doses, induction times, and ratings are shown in Table 3. All patients in the morphine group and all but three of the fentanyl-treated patients received the entire calculated induction dose of narcotic. However, 47% of the sufentanil-treated patients became unresponsive with less than the calculated 1.5 μg/kg of the drug; hence the entire loading dose was not given. Fifty percent of the meperidine-treated patients also did not receive the planned induction dose (Table 3). In four of these (25% of the group), the cause was hypotension and in one patient inability to ventilate (possible causes are laryngeal spasm or chest wall rigidity). Five (31%) meperidine-treated patients developed tachycardia,

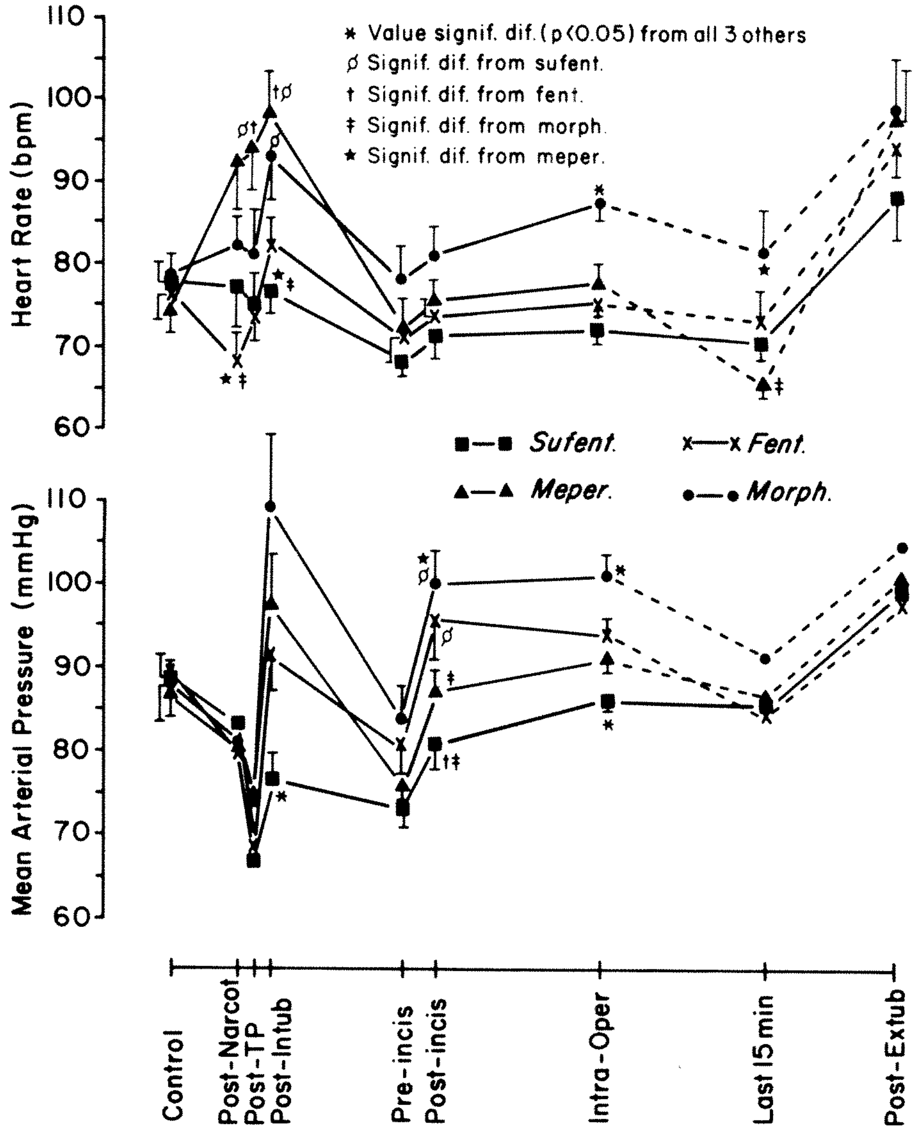


Figure 1. Mean values ± SEM for heart rate (*top*) and mean arterial blood pressure (*bottom*) before induction (Control), after narcotic administration (Post Narcot), immediately after thiopental but before succinylcholine (Post-TP), 1–2 min after intubation (Post-Intub), before and 1–2 min after incision (Pre- and Post-Incis), intraoperatively (Intra-Oper), during the last 15 min before muscle relaxant reversal (Last 15 min), and 1–2 minutes after extubation (Post-Extub). The intraoperative point is a minute-to-minute average of hemodynamic values for the first 75 min after incision for all patients before failout (see text). The average values for the last 15 min include only those patients who have not failed out. Post extubation points again include all patients. Symbols denote differences among groups. Significant intragroup changes from control or caused by events are described in the text.

accompanied in three cases by marked flushing. These five patients later were found to have abnormally elevated plasma histamines (above 1 ng/ml) after the induction dose of meperidine. Similar clinical signs and an elevated plasma level of histamine also occurred in one patient receiving morphine but were present in none of the patients receiving fentanyl or sufentanil.

Means of the mean arterial blood pressure (Fig. 1) were unchanged from the control after narcotic administration but then decreased transiently but significantly ($P < 0.05$) in all groups after the addition of thiopental (mean dose 2.08 ± 0.13 mg/kg in all; no intergroup differences). Blood pressure rose with intubation in all groups. However, mean pressures after intubation were significantly greater than the control only in the morphine group ($P < 0.02$). Mean heart rate (Fig. 1) decreased to 68 ± 3 beats/min after fentanyl induction ($P < 0.001$ compared to control). In contrast, heart rate increased by 23% to 92 ± 6 beats/min ($P < 0.01$) after meperidine, and continued to increase further in this group after thiopental and intubation. This tachycardia in the meperidine-treated patients was accompanied by a significant elevation of plasma levels of norepinephrine (Fig. 2) and epinephrine (Fig. 3) to 194 ± 21% and 678 ± 164% of the control, respectively. Otherwise, plasma levels of both catecholamines remained low in all groups throughout induction and the period prior to incision. After intubation, rate–pressure products (Fig. 4) increased significantly above the control values only in the patients receiving meperidine ($P < 0.01$) and mor-

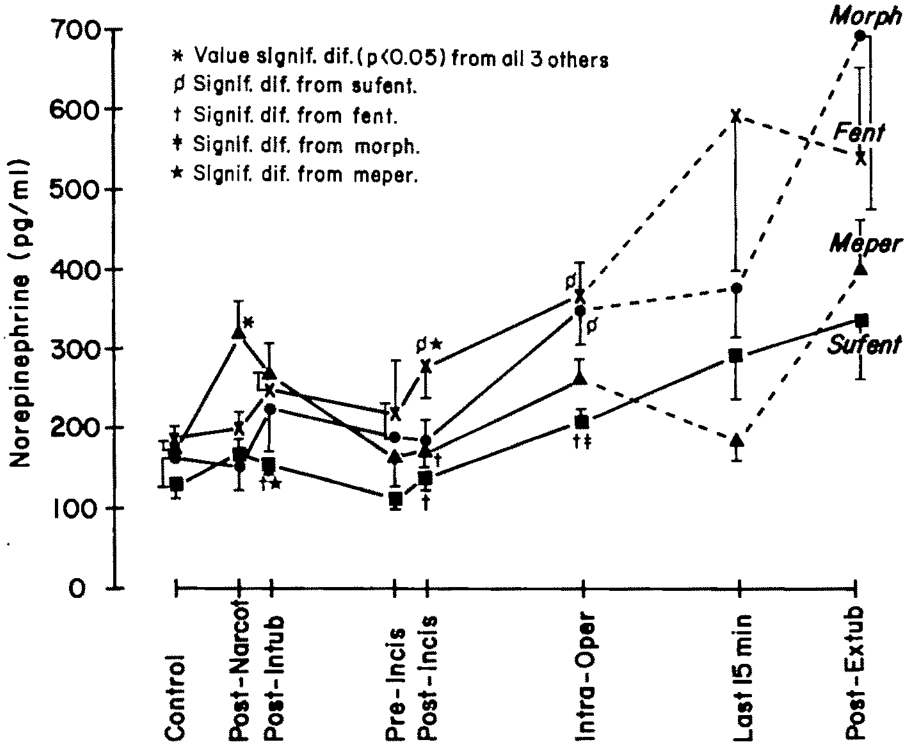


Figure 2. Mean ± SEM arterial plasma norepinephrine levels. Intervals as in Figure 1. In this figure, the intraoperative and last 15 min values were determined by averaging all norepinephrine levels taken from a patient (during the first 75 min postincision or the last 15 min, respectively) and then determining the group mean from these average values. Symbols are as in Figure 1.

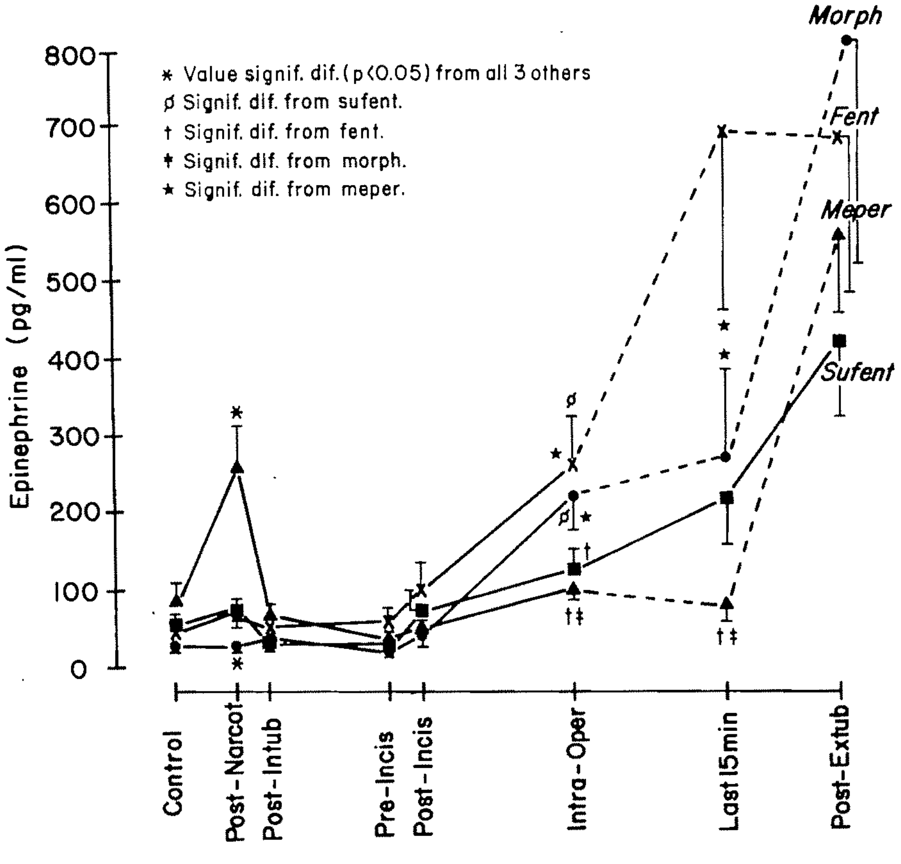


Figure 3. Mean ± SEM arterial plasma epinephrine levels. Intervals, symbols, and averaging as in Figure 2.

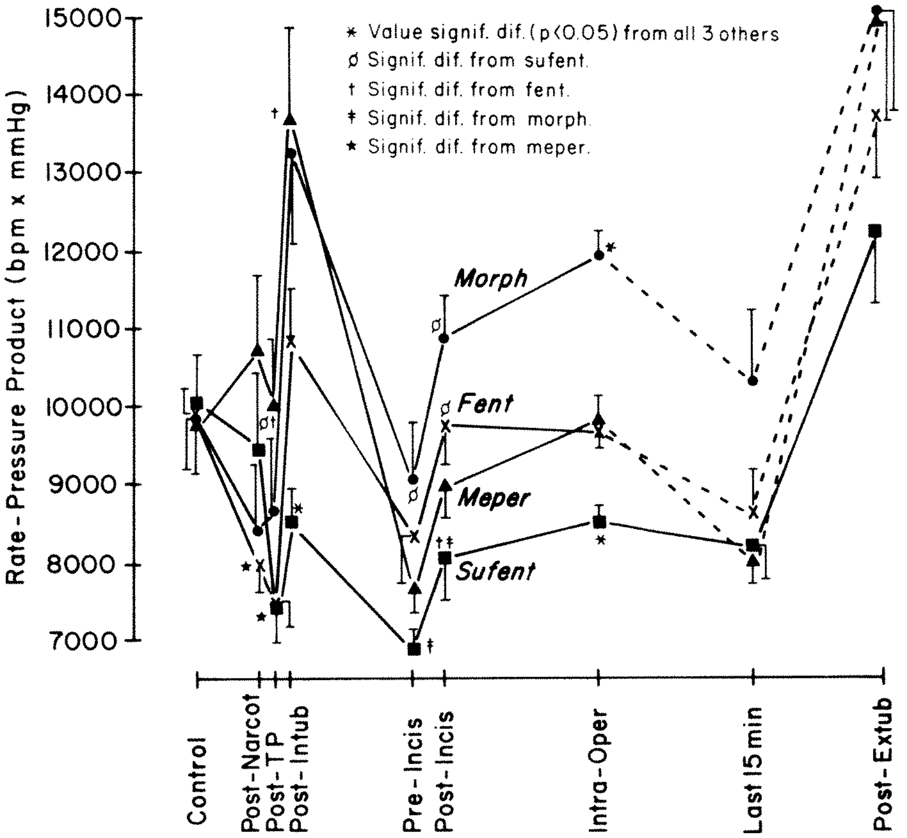


Figure 4. Mean ± SEM rate–pressure products. Time averages and symbols as in Figure 1.

phine ($P < 0.001$). Intergroup comparisons are shown in the figures.

During the period before incision, blood pressures and heart rates (Fig. 1) declined in all groups, so that the mean values for rate–pressure products before the incision returned to control levels in the fentanyl, meperidine, and morphine groups. They remained significantly below control in the sufentanil patients (Fig. 4). Skin incision caused significant increases in blood pressure (not in heart rate) in all groups (Fig. 1), but rate–pressure products after incision (Fig. 4) were not significantly different from control values in any group. Mean levels of plasma epinephrine (Fig. 3) and norepinephrine (Fig. 2) did not increase significantly with skin incision in any group.

## *Maintenance of Anesthesia*

Total doses of opioids given and the timing of the supplements are seen in Table 4. The mean total dose of thiopental in all 60 patients was 3.4 ± 0.28 mg/kg, including the induction dose (no intergroup differences); the mean concentration of nitrous oxide was 62.5 ± 0.67% (no differences); and 54 of the 60 patients received pancuronium (mean dose of 5.3 ± 0.3 mg; no differences among groups). In several patients receiving meperidine, morphine, and fentanyl, heart rate, blood pressure, or both could not be kept within 15% of the control value by additional doses of narcotic; hence, a potent inhalation agent was added (Table 4), no more narcotic was given, and no more hemodynamic data or catecholamine samples taken until the recovery period. There were no failouts in the sufentanil-treated group.

The mean percent changes in cardiovascular and catecholamine values brought about by supplementary doses of the opioids are shown in Figure 5. Overall, the most consistent responses, in frequency as well as magnitude, were seen after sufentanil with mean arterial pressure declining after 40 of 54 supplements (72%), heart rate decreasing after supplements 57% of the time, and rate–pressure product decreasing after 72%. In the groups receiving morphine, meperidine, and fentanyl, drug supplements decreased rate–pressure products only 51%, 50%, and 62% of the time, respectively. Plasma catecholamine levels 5 min after additional doses of opioid were quite variable (shown by large standard errors in Fig. 5) without significant intergroup differences.

Cardiovascular function intraoperatively also was assessed by averaging blood pressures, heart rates, and rate–pressure products for each patient every minute for the first 75 min after incision (Figs. 1,4). Intraoperative assessment was not evaluated for a longer period than this because of increasing differences in surgical manipulation, rate of blood loss, and number of patients who failed out. All catecholamine samples drawn during this 75-min period were averaged for each patient, and the means for each drug group were plotted and compared (Figs. 2,3). During this intraoperative period, heart rate was significantly greater in patients given morphine than in those in the other three groups (Fig. 1), among which there were no differences. Blood pressure was consistently and significantly lower in patients given sufentanil than in those given the other drugs, as was rate–pressure product (Figs. 1,4). Blood pressure and rate–pressure product were significantly greater in patients given morphine than in patients in the other three groups (Fig. 4). By the last 15 min of the operation, at a time when the patients who were more difficult to control had failed out in the fentanyl, meperidine, and morphine groups (approximately 30% in each group, see Table 4), all intergroup differences among the remaining patients had disappeared. Hemodynamic and catecholamine values for all patients (including failouts) were increased markedly at 1–2 min postextubation, so that mean rate–pressure products and norepinephrine and epinephrine levels were significantly greater than the control in all groups, without significant intergroup differences (Figs. 1–4).

Intraoperative plasma norepinephrine levels (Fig. 2) were lower in sufentanil-treated patients than in those receiving morphine or fentanyl but not lower than the levels in those receiving meperidine. Epinephrine levels (Fig. 3) also were highest in fentanyl-treated and morphine-treated patients. Again, intergroup differences were absent during the last 15 min.

There was a significant correlation between log concentrations of norepinephrine and epinephrine vs heart rate in all four narcotic groups (Table 5). Significant correlations between plasma catecholamine concentrations vs mean arterial pressure were not found in all drug groups.

The incidence and distribution of cardiovascular disturbances and other side effects throughout the entire study period are depicted in Table 6, in which it is seen that both disturbing and nondisturbing events occurred most frequently in the meperidine-treated patients and least frequently in the sufentanil-treated patients. Hypotension (in 63%) and tachycardia (in 56%) occurred most frequently in patients given meperidine but also occurred in patients given sufentanil and morphine. Elevations in plasma histamine to abnormal levels (>1 ng/ml) occurred in five (31%) of the

Table 4. Maintenance Doses, Times, and Requirement for Inhalational Supplementation

| | Narcotic dose | | | | Supplements | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Dose·kg⁻¹·hr⁻¹ (after induction dose) | | | | | | | |
| Drug | Total dose per kg | All patients | Failouts | Non failouts | Time to first supplement (min)[a] | Total number of supplements | Supplements per patient | Time between supplements (min)[b] | Number who received inhal agent |
| Sufentanil | 2.4 ± 0.4 μg | 0.35 ± 0.08 μg | — | — | 44.1 ± 5.0 | 54 | 3.2 | 26.9 ± 2.0 | 0 |
| Fentanyl | 15.1 ± 1.1 μg | 3.83 ± 0.61 μg | 6.47 ± 1.28 μg | 2.73 ± 0.39 μg | 35.7 ± 3.1 | 69 | 4.1 | 24.2 ± 3.0 | 5 (29%) |
| Morphine | 1.2 ± 0.1 mg | 0.32 ± 0.08 mg | 0.63 ± 0.07 mg | 0.19 ± 0.05 mg | 19.6 ± 2.9 | 43 | 4.3 | 19.5 ± 3.6 | 3 (30%) |
| Meperidine | 7.9 ± 0.5 mg | 1.27 ± 0.26 mg | 2.0 ± 0.53 mg | 0.82 ± 0.19 mg | 41.8 ± 5.6 | 62 | 3.9 | 32.1 ± 2.6 | 6 (38%) |

[a] Significantly shorter ($P < 0.005$) time to first supplement with morphine than with other three drugs, which did not differ from one another.
[b] Significantly longer time between supplements with meperidine than with morphine.

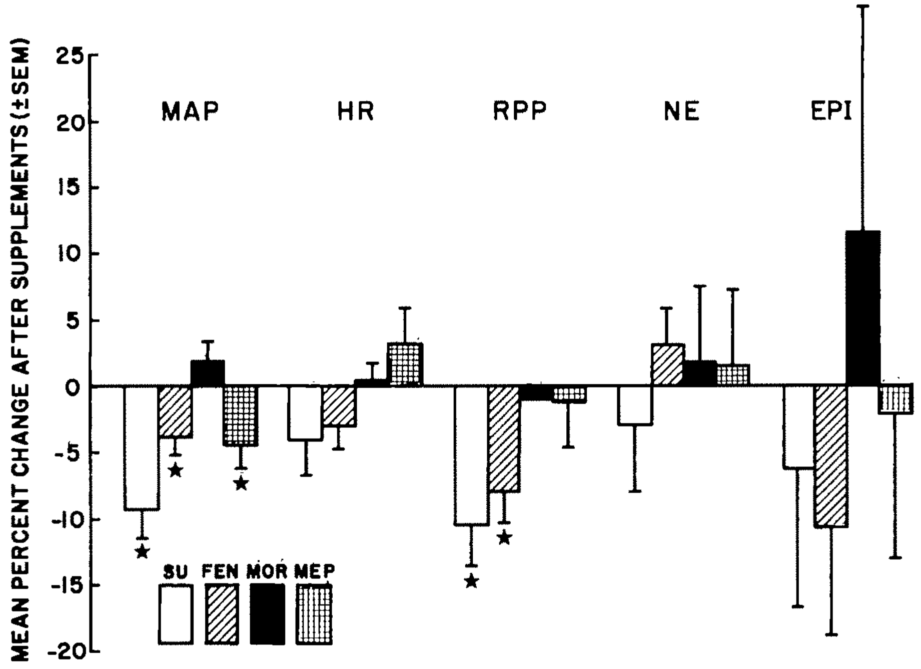


Figure 5. Effects of drug supplements on hemodynamic and plasma catecholamine values. Mean ± SEM percent changes in arterial blood pressure, heart rate (HR), rate-pressure product (RPP), and plasma catecholamine levels (NE and EPI) from just before to 5 min after narcotic supplements. Stars denote significant percent changes ($P < 0.05$). Mean pressure was decreased significantly more after sufentanil than after fentanyl ($P < 0.05$) or morphine ($P < 0.02$). Heart rate was decreased significantly more after fentanyl than after meperidine ($P < 0.05$).

patients who received meperidine and in one morphine-treated patient (Table 6). (The amounts and duration of histamine release are reported elsewhere (13).) Nondisturbing rigidity was present in four (25%) patients given meperidine and in five (29%) given sufentanil; disturbing rigidity was present in three (18%) patients given fentanyl. Disturbing hypertension was present in six (35%) fentanyl-treated and four (25%) meperidine-treated patients. Recovery room nausea and vomiting occurred least in patients given morphine. When side effects were ranked and scored (see the methods section), the overall incidence was significantly greater with meperidine than with sufentanil ($P < 0.01$) or fentanyl ($P < 0.05$).

## *Recovery*

Patients awakened promptly after discontinuation of nitrous oxide (no intergroup differences) with a mean time to return of consciousness (ability to follow commands) of 6.8 ± 1 min in all patients and of 5.5 ± 1 min in all of those who had not received an inhalation agent. However, not all patients breathed adequately unless prompted. Therefore, two patients in the group given morphine and three in the group given meperidine were taken to the recovery room while still intubated, and some patients in all groups received naloxone (Table 7). This was necessary most frequently (in 90%) and in the largest doses in patients who had received morphine, 30% of whom required intramuscular as well as intravenous naloxone. Patient number 40, who was, at age 62, the oldest participant in the study, required postoperative ventilation for several hours after attempted reversal with multiple injections of naloxone proved unsatisfactory. At this time the code was broken for the first 40 patients, and when it became apparent that nearly all the patients who had received morphine had required multiple injections of naloxone, morphine was dropped from the study. Thirty-eight percent of the meperidine-treated patients and 41% of the sufentanil-treated patients required naloxone, although the mean dose needed in the former case was much larger (see Table 7), with intramuscular doses also required in some instances. The lowest incidence of naloxone use was in the group receiving fentanyl; the lowest mean dose was in the group receiving sufentanil.

Table 7 also shows the mean times from the last dose of narcotic until the end of the case. This was significantly less for the group receiving sufentanil than for the other three groups, in all of which some patients had received an inhalation agent (and therefore no more narcotic). Narcotics were readministered to all groups except that given sufentanil, as shown by the number of sets of naloxone injections required. (One set of injections of naloxone was 1.5 μg/kg followed in 3 min by another 1.5 μg/kg.) Mean arterial $P_{CO_2}$ before all doses of naloxone was 55.1 ± 1.1 torr and did not differ among groups. At the time of discharge from the recovery room, mean $P_{CO_2}$ in all patients was 43.6 ± 0.6 torr without intergroup differences or differences between those who had received naloxone and those who had not.

Opioid medication for pain was given during the

Table 5. Regression Analyses for Heart Rate ($y$) Versus Log Plasma Catecholamines ($x$) ($y = mx + b$)

| Drug | log NE vs HR | log EPI vs HR |
|---|---|---|
| Sufentanil | | |
| Slope ($m$) | 21.2 | 9.0 |
| Intercept ($y$) | 27.0 | 58.0 |
| Correlation coefficient ($r$) | 0.46 | 0.39 |
| $P$ | <0.001 | <0.001 |
| Fentanyl | | |
| Slope ($m$) | 25.0 | 13.1 |
| Intercept ($y$) | 15.0 | 51.0 |
| Correlation coefficient ($r$) | 0.43 | 0.60 |
| $P$ | <0.001 | <0.001 |
| Morphine | | |
| Slope ($m$) | 33.2 | 8.6 |
| Intercept ($y$) | 6.0 | 70.0 |
| Correlation coefficient ($r$) | 0.65 | 0.32 |
| $P$ | <0.001 | <0.02 |
| Meperidine | | |
| Slope ($m$) | 44 | 16.0 |
| Intercept ($y$) | −14.7 | 51.0 |
| Correlation coefficient ($r$) | 0.48 | 0.43 |
| $P$ | <0.001 | <0.001 |

Correlation between log plasma catecholamine concentrations (in pg/ml) and heart rate (beats/min). $P$ values represent the level of significance for the correlation shown.

Table 6. Side Effects Observed in Different Drug Groups

| Side effect | Sufentanil | Fentanyl | Morphine | Meperidine |
|---|---|---|---|---|
| Rigidity | | | | |
| Disturbing | 0 | 3 | 0 | 1 |
| Nondisturbing | 5 | 1 | 1 | 4 |
| Hypotension | | | | |
| Disturbing | 2 | 1 | 2 | 5 |
| Nondisturbing | 2 | 6 | 3 | 5 |
| Hypertension | | | | |
| Disturbing | 1 | 6 | 1 | 4 |
| Nondisturbing | 1 | 4 | 2 | 3 |
| Bradycardia | | | | |
| Disturbing | 1 | 0 | 0 | 0 |
| Nondisturbing | 1 | 2 | 1 | 1 |
| Tachycardia | | | | |
| Disturbing | 2 | 0 | 3 | 3 |
| Nondisturbing | 1 | 1 | 3 | 6 |
| Histamine release | | | | |
| Disturbing | 0 | 0 | 1 | 4 |
| Nondisturbing | 0 | 0 | 0 | 1 |
| Nausea or vomiting in recovery room | | | | |
| Disturbing | 1 | 3 | 1 | 3 |
| Nondisturbing | 3 | 0 | 0 | 1 |
| Maximum possible[a] | 119 | 119 | 70 | 112 |

[a] Maximum possible side effects for a particular narcotic group is 7 times the number of patients receiving that drug.

The number of patients in whom disturbing (D) and nondisturbing (ND) side effects occurred is listed for each side effect. Criteria assessment as follows: rigidity, ND if able to ventilate with difficulty, D if not able to ventilate at all; nausea, ND; vomiting, D; abnormal plasma histamine (>1 ng/ml) alone, ND, if accompanied by hypotension and tachycardia, D. Hemodynamic evaluations were made subjectively by the anesthesiologist depending upon their frequency and severity. Two patients receiving sufentanil, one receiving fentanyl, two receiving meperidine, and one receiving morphine received one dose each of a vasopressor. One patient receiving sufentanil, one receiving meperidine, and one receiving morphine received one dose each of atropine.

recovery room period to six sufentanil-treated patients (one of whom had received naloxone) at a mean time of 154 ± 18 min after the last dose of sufentanil. Three fentanyl patients (given no naloxone) received pain medication 229 ± 86 min after the last narcotic dose, as did one meperidine patient, 279 min after the last dose. Reversal with naloxone caused pain severe enough to require prompt medication in two of the morphine-treated patients.

The anesthesiologists rated the emergence and recovery period as good or satisfactory in 100% of the patients given sufentanil, 93% of the patients given fentanyl, 88% of the patients given meperidine, but in only 60% of those given morphine, because of prolonged respiratory depression. Patients gave themselves good or satisfactory recovery ratings 100% of the time except for those in the morphine group, in which these ratings were given by only 60%. The reason given for this was the presence of a "drugged" or very drowsy feeling. Recovery room pain was rarely mentioned. There was no awareness or recall of the intraoperative period by any patient in any drug group.

The anesthesiologists' estimations as to which individual opioid had been given were correct in 52% of the cases. They chose the correct group of drugs, i.e., less potent, long-acting (meperidine, morphine) vs more potent, and short-acting (sufentanil, fentanyl), 67% of the time.

## Discussion

Balanced anesthesia, that is nitrous oxide in oxygen supplemented by a narcotic, small doses of a hypnotic, or both, has become a popular form of general anesthesia. In our study, it was successful 77% of the time, as shown by the fact that only 14 out of 60 patients required the addition of a potent inhalation agent, despite the fact that neither the narcotic used nor its concentration was known to the anesthesiologist. The purpose of this double-blind study was to compare, by means of a rigid protocol, the abilities of four narcotics of differing strengths and pharmacokinetic properties to provide hemodynamic and autonomic stability during balanced anesthesia. We based

Table 7. Naloxone Requirements

| | | Time from last dose narcotic until $N_2O$ off (min) | | | | No. of patients receiving naloxone | | | Dose naloxone ($\mu$g/kg) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Drug | *n* | In all | If no inhalation agent | To recovery room intubated | Ventilated | IV | IM | Inhalation agent and naloxone | IV | IM | No. of sets of injections (No. of patients) |
| Sufentanil | 17 | 45 ± 4.8[a] | (same) | 0 | 0 | 7 (41%) | 0 | 0 | 1.8 ± 0.3 | 0 | 1 injection in all |
| Fentanyl | 17 | 94 ± 19.1 | 60 ± 8.6 | 0 | 0 | 3 (18%) | 0 | 0 | 3.2 ± 1.2 | 0 | 1 (1 patient)<br>2 (1 patient)<br>3 (1 patient) |
| Morphine | 10 | 79 ± 10.9 | 63 ± 7.2 | 2 | 1 | 9 (90%) | 3 (30%) | 3 | 3.5 ± 1.2 | 5.1 ± 0.8 | 1 (4 patients)<br>2 (1 patient)<br>4 (1 patient)<br>5 (2 patients)<br>7 (1 patient) |
| Meperidine | 16 | 94 ± 17.8 | 56 ± 8.6 | 3 | 0 | 6 (38%) | 1 (6%) | 2 | 4.7 ± 0.4 | 2.8 | 1 (3 patients)<br>2 (1 patient)<br>3 (1 patient)<br>5 (1 patient) |

Mean values ± SEM.

[a] Significantly less time than with other three agents ($P < 0.02$ or less).

our observations on continuous blood pressure and heart rate measurements during operation and by retrospective analysis of arterial plasma catecholamine levels. We found that under these special circumstances, the more potent agents with a shorter onset of action (sufentanil and fentanyl) were more effective than the less potent ones with a longer latency (morphine and meperidine). Indeed, greater than customary clinical loading doses of the latter drugs failed to suppress excitatory cardiovascular responses to intubation and incision. Although insufficient time between the administration of these longer-acting drugs and intubation may be blamed for their lack of efficacy at this time, the more than 30 min that elapsed before incision should have allowed ample time for both agents to attain their maximal effect. In addition, induction with meperidine caused complications, i.e., hypotension and tachycardia, in half the patients (Fig. 1, Table 6). In most of these patients (Table 6), these changes were shown to be associated with histamine release, an unsurprising phenomenon in view of the literature (15). The inability to prevent intraoperative hypertension and tachycardia with morphine, meperidine, or fentanyl (Figs. 1,4), which necessitated the addition of a potent inhalational agent in approximately 30% of the patients in these groups (Table 4), stands in contrast to the situation in the group of patients given sufentanil, in which they demonstrated the least hemodynamic (Figs. 1,4) and sympathoadrenal (Figs. 2,3) activity intraoperatively. Hence, additional inhalation supplementation was not needed. Again, the slower onset of action of morphine, meperidine, and fentanyl (3,4) compared to sufentanil, may have been responsible for this. Certainly it did seem as if the promptness, as well as the magnitude (Fig. 5), of response to sufentanil supplements was greater than it was to the other three drugs, thus making it possible to control more rapidly the unexpected increases in hemodynamic activity. However, at the time of emergence and extubation, all patient groups showed comparable signs of cardiovascular and adrenergic neuroendocrine stimulation (Figs. 1–4).

It is important to note that no matter which narcotic was used, increased heart rate was accompanied by the release of norepinephrine or epinephrine (Table 5). This would imply that none of the four narcotics studied affects the response to catecholamines once they have been released. It therefore becomes important to know which narcotic best suppresses catecholamine release during stressful operative periods. In this investigation, sufentanil and meperidine resulted in the lowest intraoperative plasma levels. The effect of the catecholamines on heart rate was approximately the same in the sufentanil-, fentanyl-, and morphine-treated groups. It is of interest that the effects of catecholamines were greater (slope of log catecholamine level vs heart rate) in the meperidine group. The mild vagolytic action of this narcotic (16) may have contributed to the tachycardiac effect in these patients.

Although there have been a number of previous studies (17–22) comparing narcotic agents in low or moderate doses, few were blind, and none simultaneously compared all four drugs used in this study. The only other study in which all four of these narcotics have been compared in a double-blind manner is one by Ghoneim et al. (23), in which our induction and maintenance protocol was used. These investigators did not find differences among agents to be as clear cut, nor did they have the high incidence of failout that we had. As their patients' operation types and times, and the total doses of opiates used were nearly identical to ours, we can explain the differences in results only by the fact that these investigators did not measure hemodynamic values continuously, as we did, but rather by intermittent sphygmomanometry, which may have made recognition of transient but marked deviations from baseline difficult or impossible. In a nonblinded comparison of fentanyl and sufentanil during anesthesia for craniotomy in which radial arterial pressure was also measured continuously, McKay et al. (21) also reported better blood pressure control with sufentanil. We found continuous recording of hemodynamic values a great help in determining cardiovascular and autonomic stability during periods of surgical stimulation. Ghoneim et al. (23) did not find any intergroup differences in plasma levels of norepinephrine. This is probably due to the fact that they sampled venous (perhaps forearm), instead of arterial blood and not at precisely stated times. Several investigative groups recently have demonstrated that catecholamine extraction during passage through the vascular bed of different organs (difference between arterial and venous concentrations) may vary considerably, even in the same organ at different times (24–28). This, and the very short halflife (24–28) of circulating catecholamines (60–80 sec), makes venous sampling a poor choice if one is interested in a correlation between adrenergic neurohumoral activity and plasma levels.

As it is well known that patients differ in their requirements for and responses to narcotics (and other central nervous system drugs), we decided to titrate our drugs to effect during the induction rather than to give a fixed amount, that is, to let the patient tell us what he or she needed. This titration would tend to correct any possible errors in our literature-based (3,7,9,17–22,29,30), but unavoidably somewhat arbitrary, assignment of potency ratios. In addition, if relative overdoses were given, these would last longer, and thus supplementary doses would not be called for as soon. This seems to be borne out by the fact that, although the concentration of our opiate solutions was chosen based upon an arbitrarily assigned potency ratio of fentanyl to morphine (80:1) and of sufentanil to fentanyl (5:1), the actual usage under blind conditions of these agents, after the induction dose, turned out to be morphine to fentanyl, 84:1, but fentanyl to sufentanil, 11:1 (Table 4). In other words, the potency of sufentanil to fentanyl during maintenance was nearly twice as much as we had assumed when we planned our induction doses. Total amounts (induction plus maintenance) of these two drugs given indicate that seven times more fentanyl was required than sufentanil. Remarkably, another double-blind comparison of these three agents by Kay and Rolly (20), resulted in similar overall use of seven times as much fentanyl as sufentanil, in spite of the fact that the ratio of their induction loading doses was 10 times as much fentanyl as sufentanil. This would seem to indicate that in two separate studies, differing in opposite direction in the relative size of the induction doses, the observed ratio of total doses was 7:1 (fentanyl:sufentanil).

The relatively greater amount of sufentanil given during induction in the present study probably accounts for the fact that the mean interval before the first supplement of this allegedly shorter acting (3–5) agent was equally as long as that seen with fentanyl or meperidine (Table 4). The shortest interval before the first supplement was seen in patients receiving the longer-acting drug, morphine. We attribute this to the relative ineffectiveness of this agent, even after what we felt was a substantial loading dose of 0.6 mg/kg; however, perhaps we overestimated the potency of morphine. In the case of meperidine, the mean induction dose of 4.3 mg/kg actually given still permitted frequent untoward hemodynamic and catecholamine changes during intubation (see Figs. 1–4). Once this potent stimulus was over, however, this dose was sufficient to carry the patients more than twice as long as the initial morphine dose. In fact, dosage intervals between subsequent supplements remained the shortest for morphine, perhaps again caused by the fact that we never really achieved effective control of autonomic, sympathetic activity, and hence of cardiovascular parameters, with this drug in the doses used, and thus felt obliged to administer supplements more frequently and at shorter intervals before giving up. In the study by Holmes (18), in which he compared morphine, meperidine, and fentanyl, mean morphine use was at the rate of 324 $\mu g \cdot kg^{-1} \cdot hr^{-1}$, a figure nearly identical to the 320 $\mu g \cdot kg^{-1} \cdot hr^{-1}$ in the present investigation (Table 4). Holmes's patients also received nearly identical amounts of fentanyl as ours (3.6 vs 3.8 $\mu g \cdot kg^{-1} \cdot hr^{-1}$), but he gave nearly twice as much meperidine on basis of time. Cardiovascular measurements in Holmes's study (18) showed no intergroup differences, but again this may have been due to the intermittent method of measurement.

In spite of prompt return of consciousness, respiratory depression was still present in many patients of all groups. However, it was unquestionably greatest in those patients receiving morphine, as shown by the frequency and magnitude of naloxone administration (Table 7). This was the case whether or not the patients had received an inhalation agent. The addition of an inhalation agent meant, of course, that the interval between the last opiate dose and emergence was greater (Table 7). Moreover, some morphine patients themselves were unhappy because of their state of drowsiness during recovery. This was not so with patients receiving meperidine, who, although requiring an even larger mean intravenous dose of naloxone than patients given morphine, were satisfied with their recovery; that is, they were apparently unaware that they were still depressed. This subjective lack of concern with their actual state by patients who have received meperidine, seen both during induction and during recovery in the present investigation, was also reported for the recovery period by Ghoneim et al. (23). For reasons unknown, meperidine seems to have certain qualities that make it different from the other narcotics in other aspects as well (31,32). Patients who had received fentanyl or sufentanil were the most alert and had the least respiratory depression (Table 7). Although 41% of the patients in the sufentanil-treated group required narcotic reversal, compared to only 18% of those who had received fentanyl, there was no evidence of renarcotization in these seven sufentanil patients (i.e., they required only one set of naloxone injections). The mean total dose of naloxone was lower than in the fentanyl group (Table 7). This and the fact that the sufentanil patients required postoperative pain medication sooner, fits with the reported shorter elimination half-life for sufentanil than for fentanyl (5). The relatively high incidence of need for reversal after sufentanil was due partly to the fact that the mean time since administration of the last dose of narcotic was only 45 min, significantly shorter than in all other drug groups (Table 7). This shorter interval was, of course, attributable to the fact that no inhalation agents were given to the sufentanil patients. A time differential remained even when the inhalation group was excluded (Table 7), but it was not statistically significant. In comparison with other blind studies, the patients in this one required more naloxone than those of Holmes (18), but his narcotic doses were considerably less than ours. The patients studied by Ghoneim and et al. (23) received the same doses of opiates as did ours, but only six of their 64 required reversal, and only one of these patients had received morphine. Although their criteria for respiratory depression and for administering naloxone are not given (nor are the doses), we can speculate that the discrepancy in the ages of the patients in two studies (mean, 27 yr in theirs; 40 yr in ours) may have been partly responsible for the considerable disparity. Stimulation during the recovery period, provided by postoperative testing, also may have helped to prevent respiratory depression in their patients. In contrast, our patients were deliberately observed while undisturbed in the recovery room in an effort to simulate the probable situation after return to their rooms.

In summary, we have found clear differences during balanced anesthesia among four opiates of different potencies and durations of action under careful double-blind conditions. Overall, the most satisfactory conditions during induction of anesthesia, intraoperatively, and during recovery were seen with sufentanil. In fact, within the rigid guidelines imposed by our study protocol, which we feel were necessary for purposes of interdrug comparison, it was possible to adequately control blood pressure and heart rate intraoperatively only with sufentanil. Meperidine was most unsatisfactory as an induction agent because of the high incidence of histamine release, hypotension, and tachycardia. Morphine was the least satisfactory drug in controlling hemodynamics during the operation. Intraoperative sympathoadrenal activity was less when sufentanil and meperidine were used than when the other two drugs were used. Recovery was least satisfactory with morphine because of residual respiratory depression. With less strict criteria for control of hemodynamics, intergroup differences might have been less marked, as in the work of others (18,22,23).

The authors would like to thank the patients' surgeons and the operating room and recovery room nurses for their vital and generous cooperation. In addition, we gratefully acknowledge the expertise of Rose Antonucci in the preparation of the manuscript and the long hours spent compiling statistics by Jane Ball.

## References

1. Alper MH, Flacke W. The peripheral effects of anesthetics. Ann Rev Pharmacol 1969;9:273–96.
2. De Castro J. Practical applications and limitations of analgesic anesthesia. A review. Acta Anaesthesiol Belg 1976;27:107–28.
3. de Lange S, Boscoe MJ, Stanley TH, Pace N. Comparison of sufentanil-$O_2$ and fentanyl-$O_2$ for coronary artery surgery. Anesthesiology 1982;56:112–8.
4. Smith NT, Dec-Silver H, Harrison WK, Sanford TJ, Gillig J. A comparison among morphine, fentanyl and sufentanil anesthesia for open-heart surgery. Induction, emergence and extubation. Anesthesiology 1982;57:A291.
5. Bovill JG, Sebel PS, Blackburn CL, Heykants J. Kinetics of alfentanil and sufentanil: a comparison. Anesthesiology 1981;55:A174.
6. De Castro J, Van de Water A, Wouters L, Xhonneux R, Reneman R, Kay B. Comparative study of cardiovascular, neuro-

logical, and metabolic side effects of eight narcotics in dogs. Acta Anaesthesiol Belg 1979;30:6–96.

7. Stanley TH, Webster LR. Anesthetic requirements and cardiovascular effects of fentanyl-oxygen and fentanyl-diazepam–oxygen anesthesia in man. Anesth Analg 1978;57:411–26.
8. Rosow CE, Moss J, Philbin DM, Savarese JJ. Histamine release during morphine and fentanyl anesthesia. Anesthesiology 1982;56:93–6.
9. Jaffe JH, Martin WR. Opioid analgesia and antagonists. In: Gilman AG, Goodman LS, Gilman A, eds. The pharmacological basis of therapeutics, 6th ed. New York: Macmillan, 1980:518.
10. Watson E. Liquid chromatography with electrochemical detection for plasma norepinephrine and epinephrine. Life Sci 1981;28:493–7.
11. Moss J, Rosow CE, Savarese JJ, Philbin DM, Kniffen KJ. Role of histamine in the hypotensive action of *d*-tubocurarine in humans. Anesthesiology 1981;55:19–25.
12. Flacke JW, Kripke BJ, Bloor BC, Flacke WE, Katz RL. Intraoperative effectiveness of sufentanil, fentanyl, meperidine, or morphine in balanced anesthesia: a double-blind study. Anesth Analg 1983;62:259–60.
13. Flacke JW, Van Etten A, Flacke WE. Greatest histamine release from meperidine among four narcotics. Double-blind study in man. Anesthesiology 1983;59:A51.
14. Flacke JW, Kripke BJ, Bloor BC, Flacke WE. Comparison of opioids in balanced anesthesia, a discussion of a presentation by Dr. NH Fahmy at Cleveland Clinic Symposium on Opioids in Anesthesia. In: Estafanous FG, ed. Opioids in anesthesia. Boston: Butterworth, 1984;140–5.
15. Finer BL, Partington W. Pethidine and the triple response. Br Med J 1953;1:431–3.
16. Gruber CM, Hart ER, Gruber CM Jr. The pharmacology and toxicology of the ethyl ester of 1-methyl-4-phenyl-piperidine-4-carboxylic acid (demerol). J Pharmacol Exp Ther 1941;73:319–4.
17. Clark N, Liu WS, Meuleman T, Zwanikken P, Pace NL, Stanley TH. Sufentanil versus fentanyl as a supplement to $N_2O$ anesthesia during general surgery. Anesth Analg 1984;63:198.
18. Holmes CM. Supplementation of general anaesthesia with narcotic analgesics. Br J Anaesth 1976;48:907–13.
19. Kalenda Z, Scheijgrond HW. Anaesthesia with sufentanil-analgesia in carotid and vertebral arteriography. A comparison with fentanyl. Anaesthetist 1976;25:380–3.
20. Kay B, Rolly G. Duration of action of analgesia supplements to anesthesia. A double-blind comparison between morphine, fentanyl and sufentanil. Acta Anesthesiol Belg 1977;28:25–32.
21. McKay RD, Varner PD, Hendricks PL, Adams ML, Harsh GR. The evaluation of sufentanil-$N_2O$-$O_2$ vs fentanyl-$N_2O$-$O_2$ anesthesia for craniotomy. Anesth Analg 1984;63:250.
22. Van De Walle J, Lauwers P, Adriaensen H. Double blind comparison of fentanyl and sufentanil in anesthesia. Acta Anaesthesiol Belg 1976;27:129–38.
23. Ghoneim MM, Dhanaraj J, Choi WW. Comparison of four opioid analgesics as supplements to nitrous oxide anesthesia. Anesth Analg 1984;63:405–12.
24. Hilstead J, Christensen NJ, Madsbad S. Whole body clearance of norepinephrine. The significance of arterial sampling and of surgical stress. J Clin Invest 1983;71:500–5.
25. Best JD, Halter JB. Release and clearance rate of epinephrine in man: importance of arterial measurements. J Clin Endocrinol Metab 1982;55:263–8.
26. Hjemdahl P, Freysehnss U, Juhlin-Darmfelt A, Linde B. Differential sympathetic activation during mental stress evoked by Stroop test. Acta Physiol Scand (Suppl) 1984;527:25–9.
27. Flacke WE, Van Etten A, Bloor BC. Plasma catecholamine levels during surgical removal of pheochromocytomas. Abstracts of IX International Congress Pharmacology, London 1984;172.
28. Flacke WE, Flacke JW, Bloor BC. Adrenal Medulla. Seminars in Anesthesia 1984;3:;194–206.
29. De Castro J. Use of sufentanil in analgesic anaesthesia. In: VI Congress Mondial d'Anesthesiologie, Mexico, 1976. Anesthesie et reanimation pratique. Societé d'Anesthesiologie de Charleroi 1976;6:96–114.
30. Hug CC. What are the roles of narcotic analgesic anesthesia? In: Hershey SG, ed. ASA refresher courses in anesthesiology, vol. 9. Philadelphia: J. B. Lippincott, 1980:71–83.
31. Burks LC, Aisner J, Fortner CL, Wiernik PH. Meperidine for the treatment of shaking chills and fever. Arch Intern Med 1980;140:483–4.
32. Roy RC, Pauca AL, Savage RA, Simpson S. Meperidine, not fentanyl or morphine stops postanesthetic shivering. Anesthesiology 1983;59:A349.

ANESTH ANALG
1985;64:911–6

# Bupivacaine Cardiovascular Toxicity:

## Comparison of Treatment with Bretylium and Lidocaine

Gregory W. Kasten, MD, and Stuart T. Martin, MD, PhD

KASTEN GW, MARTIN ST. Bupivacaine cardiovascular toxicity: comparison of treatment with bretylium and lidocaine. Anesth Analg 1985;64:911–6.

*Using anesthetized dogs, this study compared treatment with lidocaine or bretylium for bupivacaine-induced cardiovascular toxicity. Pentobarbital-anesthetized and -ventilated dogs ($n = 10$) were given a bolus dose of bupivacaine, 4 mg/kg, and a constant infusion of 0.2 $mg \cdot kg^{-1} \cdot min^{-1}$ to produce steady-state serum levels of 7.1 ± 1.8 μg/ml of bupivacaine. Using burst ventricular pacing, the ventricular tachycardia threshold was determined, along with hemodynamic and electrophysiologic parameters. The animals were then treated with bretylium, 20 mg/kg ($n = 5$), or lidocaine, 2 mg/kg, followed by a continuous infusion of lidocaine, 0.1 $mg \cdot kg^{-1} \cdot min^{-1}$ ($n = 5$). Bupivacaine-induced alterations in cardiac output, stroke volume, heart rate, and systemic vascular resistance were corrected by bretylium but not lidocaine. Bupivacaine caused a significant lowering of the ventricular tachycardia threshold, which was consistently raised by bretylium, while lidocaine was either ineffective or caused a further lowering of the threshold. Bupivacaine caused a significant increase in the Q–TU interval and resulted in an undulating polymorphic ventricular tachycardia, similar to that seen in Torsades de Pointes.*

Key Words: ANESTHETICS, LOCAL—bupivacaine. HEART, ARRHYTHMIAS—bretylium. TOXICITY—bupivacaine.

Potent long-acting local anesthetics, such as bupivacaine and etidocaine, may result in cardiovascular (CV) toxicity after accidental intravenous administration during an attempt to provide regional anesthesia (1,2). The most important aspect of this problem is the prevention of intravascular injection of these drugs, but also a rational treatment of the ventricular arrhythmias is required. Unfortunately, treatment of ventricular arrhythmias caused by long-acting potent local anesthetics has not been fully investigated to date.

Because lidocaine acts at a similar site in the cardiac membrane as bupivacaine, it may be ineffective for ventricular arrhythmias from potent long-acting anesthetics (3). The potent, antiarrhythmic, antifibrillatory agent bretylium may have a beneficial effect on the ventricular arrhythmias caused by bupivacaine or etidocaine, but this has not been completely investigated (4). This study compared the hemodynamic and electrophysiologic effects of bretylium and lidocaine in anesthetized dogs that were experiencing bupivacaine CV toxicity.

## Methods

Ten adult mongrel dogs weighing 18.4 ± 2.5 kg were anesthetized with intravenous sodium pentobarbital, 30 mg/kg, and paralyzed with pancuronium bromide, 0.15 mg/kg. A cuffed endotracheal tube was inserted, and the animals were ventilated with 100% oxygen using an AirShields ventilator. Tidal volume, respiratory rate, and sodium bicarbonate administration (0.5 mEq/kg at least 30 min prior to the experimental period) were adjusted to provide the following arterial blood gas values: pHa 7.35–7.45, $Pa_{CO_2}$ 32–40 mm Hg, and $Pa_{O_2}$ 300–500 mm Hg. Arterial blood gas values also were measured after administration of bupivacaine and administration of the therapeutic agent.

A left femoral arterial line was placed for arterial blood gas analysis, bupivacaine and lidocaine sampling, and direct recording of the arterial blood pressure. A five-lead pacing Swan–Ganz catheter (American Edwards model 93-200-7F) was placed through the right external jugular vein into the pulmonary artery. The position was adjusted such that the proximal leads recorded an intraatrial electrogram and the distal leads recorded the intraventricular electrogram while the ability to "wedge" the pulmonary artery was maintained. The position of the catheter was observed constantly and changed when needed to allow for continuous recording of the above parameters. Cardiac output was determined using the thermodi-

---

Funded in part by a grant from American Critical Care.

Received from the Department of Anesthesiology, University of Kentucky Albert B. Chandler Medical Center and Veterans Administration Medical Center, Lexington, Kentucky. Accepted for publication April 15, 1985.

Address correspondence to Dr. Kasten, Department of Anesthesiology, University of Kentucky Medical Center, Lexington, KY 40536-0084.

© 1985 by the International Anesthesia Research Society

lution technique and a cardiac output computer (American Edwards model 9510A). Each time the cardiac output was determined, five values were obtained and the results were averaged. The lead II surface electrocardiogram, intraatrial and intraventricular electrograms, arterial blood pressure, central venous pressure, and pulmonary artery pressure were recorded continuously on a polygraph (Grass model 7A). A sternotomy and pericardiotomy were performed to expose the epicardial surface of the heart after an additional 10 mg/kg of pentobarbital intravenously. A bipolar needle electrode was placed one cm apart in the left ventricular apex to allow for ventricular pacing. The ventricular tachycardia threshold was determined using a programmable stimulator (Medtronics model 5325) using methods similar to those in the cardiac catheterization laboratory for arrhythmia induction in humans (5) but modified as follows. Using a rectangular stimulus of 2 msec at twice the diastolic threshold, 10-sec burst pacing was done beginning at a rate of 200 beats per minute (bpm). The rate was increased by 50 bpm every minute until either ventricular tachycardia was induced or a rate of 400 bpm had been reached. Rates of greater than 400 bpm were not attempted. One minute was allowed to elapse between each period of stimulation to permit correction of hypotension due to tachycardia and washout of myocardial metabolites. The same needle electrode location and stimulus strength were used throughout the experimental period.

Bupivacaine, 4 mg/kg, was administered via intravenous bolus over a 60-sec time period, and by an infusion at a rate of 0.2 $mg{\cdot}kg^{-1}{\cdot}min^{-1}$. These doses were designed to provide a steady-state bupivacaine level of approximately 7 μg/ml throughout the experiment. Arterial blood samples for measurement of bupivacaine serum levels were obtained at the following times to confirm steady-state conditions throughout the experiment: 10 and 30 min after the initial administration of bupivacaine, after programmed stimulation of the ventricle prior to administration of bretylium or lidocaine, 10 min after the administration of bretylium or lidocaine, and after programmed stimulation of the ventricle. Arterial blood samples for measurement of lidocaine serum levels were obtained 10 min after the administration of lidocaine and after programmed stimulation of the ventricle. The method of analysis for bupivacaine and lidocaine has been described previously in detail and uses mepivacaine as the internal standard (6). After extraction of the local anesthetic, 2 μl of the solution is injected into a gas chromatograph (Packard model 430) fitted with a nitrogen phosphorous detector using a 183-cm OV-17 100-120 mesh Ultrabond column. The column detector temperature was 270°C, the injector temperature was 250°C, and the oven temperature was 245°C.

The experimental protocol was as follows: after animal preparation, 30 min were allowed to obtain baseline data before administration of bupivacaine. Lead II surface electrocardiogram, intraatrial and intraventricular electrograms, systemic arterial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, central venous pressure, and cardiac output were recorded as controls. Systemic vascular resistance, pulmonary vascular resistance, and stroke volume were calculated from these data. Using the recorded ECG lead best showing the T-wave and Q–T interval, the following parameters were recorded: heart rate, PR interval, QRS duration, and Q–TU interval.

Ventricular tachycardia threshold was then determined using the above-described method of burst ventricular pacing. After this control period, bupivacaine was administered in a bolus dose and constant infusion dose described above to provide steady-state serum levels. Thirty min after the start of bupivacaine administration, hemodynamic and electrophysiologic measurements were repeated. The ventricular tachycardia threshold was determined using burst ventricular pacing. After 10 sec of sustained ventricular tachycardia, the animals were cardioverted with 40 watt-seconds using internal paddles to return to sinus rhythm. [Cardioversion with 10 sec of sustained ventricular tachycardia allows for return of normal sinus rhythm without the need for pharmacologic therapy (unpublished observations).] Any animal in which sinus rhythm could not be restored with two attempts to cardioversion was omitted from the study. Thirty min after cardioversion, the animals were randomized into two treatment groups that received either bretylium, 20 mg/kg intravenously over 1 min, or lidocaine, 2 mg/kg intravenously over 1 min and a constant infusion of 0.1 $mg \cdot kg^{-1} \cdot min^{-1}$. Ten min after the administration of these drugs, hemodynamic and electrophysiologic measurements were repeated. The ventricular tachycardia threshold was determined again using burst ventricular pacing. The animals were then sacrificed with 100 mEq of intravenous KCl. Data analysis was done using the $\chi^2$-test, Student's *t*-test for paired data, and analysis of variance. A probability level of $P < 0.05$ was considered statistically significant.

## Results

The hemodynamic and electrophysiologic results in the control period, bupivacaine-only period, and therapeutic intervention with either bretylium (group B) or lidocaine (group L) are shown in Table 1. Pro-

Table 1. Hemodynamic and Electrophysiologic Results from Bupivacaine and Therapy[b]

| Parameter | Group | Baseline | After bupivacaine | After therapeutic agent |
|---|---|---|---|---|
| L/min CO | Group *B* | 3.7 ± 0.5 | 2.0 ± 0.7[a] | 5.5 ± 1.1[ac] |
| | Group *L* | 4.2 ± 1.1 | 2.1 ± 0.6[a] | 1.8 ± 0.4[a] |
| ml/beat SV | Group *B* | 26.5 ± 11.5 | 19.6 ± 11.1[a] | 28.5 ± 6.4[ac] |
| | Group *L* | 31.8 ± 10.2 | 21.7 ± 8.3[a] | 19.4 ± 10.5[a] |
| mm Hg MAP | Group *B* | 111.5 ± 20.1 | 105.4 ± 11.8[a] | 125.4 ± 20.1[ac] |
| | Group *L* | 107.8 ± 18.2 | 103.7 ± 12.5[a] | 97.2 ± 11.1[a] |
| dyne-sec·cm $^{-5}$ SVR | Group *B* | 2211 ± 560 | 2960 ± 1015[a] | 1750 ± 910[c] |
| | Group *L* | 1715 ± 780 | 2740 ± 910[a] | 2650 ± 700[a] |
| mm Hg MPAP | Group *B* | 14.7 ± 2.3 | 15.1 ± 3.2 | 17.5 ± 2.3[a] |
| | Group *L* | 12.9 ± 3.1 | 13.1 ± 1.9 | 15.1 ± 3.9 |
| dyne-sec·cm $^{-5}$ PVR | Group *B* | 118 ± 40 | 149 ± 30[a] | 153 ± 27[a] |
| | Group *L* | 142 ± 51 | 171 ± 33[a] | 168 ± 23[a] |
| mm Hg CVP | Group *B* | 5.6 ± 2.3 | 6.1 ± 2.1 | 6.2 ± 2.9 |
| | Group *L* | 8.1 ± 2.9 | 7.9 ± 3.0 | 7.5 ± 3.0 |
| mm Hg PCWP | Group *B* | 7.8 ± 1.1 | 9.0 ± 2.3[a] | 9.1 ± 1.7[a] |
| | Group *L* | 7.1 ± 1.1 | 10.1 ± 2.1[a] | 10.0 ± 2.6[a] |
| beats/min HR | Group *B* | 169 ± 19 | 148 ± 10[a] | 195 ± 20[a,c] |
| | Group *L* | 175 ± 21 | 143 ± 13[a] | 131 ± 18[a] |
| Sec QRS duration | Group *B* | 0.12 ± 0.02 | 0.14 ± 0.02[a] | 0.15 ± 0.02[a] |
| | Group *L* | 0.12 ± 0.03 | 0.15 ± 0.02[a] | 0.15 ± 0.03[a] |
| Sec PR interval | Group *B* | 0.10 ± 0.01 | 0.13 ± 0.02[a] | 0.14 ± 0.02[a] |
| | Group *L* | 0.11 ± 0.02 | 0.14 ± 0.01[a] | 0.14 ± 0.02[a] |
| Sec Q–TU interval | Group *B* | 0.22 ± 0.04 | 0.40 ± 0.05[a] | 0.41 ± 0.06[a] |
| | Group *L* | 0.21 ± 0.03 | 0.38 ± 0.04[a] | 0.38 ± 0.04[a] |

Group *B*, bretylium. Group *L*, lidocaine.
[a] Significance from baseline $P < 0.05$.
[b] All figures expressed as mean ± SD.
[c] Significance between group $P < 0.05$.

grammed stimulation of the ventricle resulted in no animals in either group sustaining ventricular tachycardia in the control period. The bolus and constant infusion doses of bupivacaine resulted in steady-state serum levels of 7.1 ± 1.8 μg/ml (mean ± SD) of bupivacaine throughout the experiment. There was no significant difference between beginning and ending bupivacaine serum levels, between each experimental period, nor between the bretylium and lidocaine treatment groups.

Compared to the baseline levels, bupivacaine caused a significant decrease in cardiac output, stroke volume, heart rate, mean arterial pressure, and an increase in systemic vascular resistance, pulmonary vascular resistance, and pulmonary capillary wedge pressure. The electrocardiogram changes included significant increases of the Q–TU interval, T-wave height, PR interval, and QRS duration. The electrocardiographic changes induced by bupivacaine are shown in Figure 1. Bupivacaine caused significant repolarization changes as evidenced by the formation of a U-wave, or "slow wave," following the T-wave. Despite the electrophysiologic changes induced by bupivacaine, no spontaneous arrhythmias occurred in any animals. All animals in both groups sustained ventricular tachycardia during programmed stimulation of the ventricle after the administration of bupivacaine. No animal was omitted from the study because of inability to convert the ventricular tachycardia to sinus rhythm with DC shock.

The administration of bretylium resulted in significant increases in heart rate, mean arterial pressure, cardiac output, and stroke volume, with a decrease in systemic vascular resistance. On programmed stimulation of the ventricle, the ventricular tachycardia threshold was raised in all animals, and in four of the five animals, ventricular tachycardia could not be induced at the maximum rate of 400 bpm used in this study. In one animal that experienced ventricular tachycardia after bretylium administration, the threshold was increased from 250 bpm during bupivacaine administration to 400 bpm after the administration of bretylium. These changes were statistically significant.

The administration of lidocaine resulted in serum levels of 2.0 ± 1.5 μg/ml (mean ± SD). Lidocaine resulted in a slightly decreased cardiac output and stroke volume, both being statistically significant. The Q–TU interval did not increase further after administration of lidocaine. Ventricular tachycardia oc-

Table 2. Results of Programmed Ventricular Stimulation

| | Baseline | After bupivacaine | | After therapy | |
|---|---|---|---|---|---|
| | Animals in ventricular tachycardia | Animals in ventricular tachycardia | Animals with lowered threshold | Animals in ventricular tachycardia | Animals with raised threshold |
| Lidocaine group (n = 5) | 0/5 (0%) | 5/5 (100%) | 5/5 (100%) | 5/5 (100%) | 0/5 (0%) |
| Bretylium group (n = 5) | 0/5 (0%) | 5/5 (100%) | 5/5 (100%) | 1/5[b] (20%) | 5/5[a] (100%) |

[a] $P < 0.01$ between groups.
[b] $P = 0.06$ between groups.

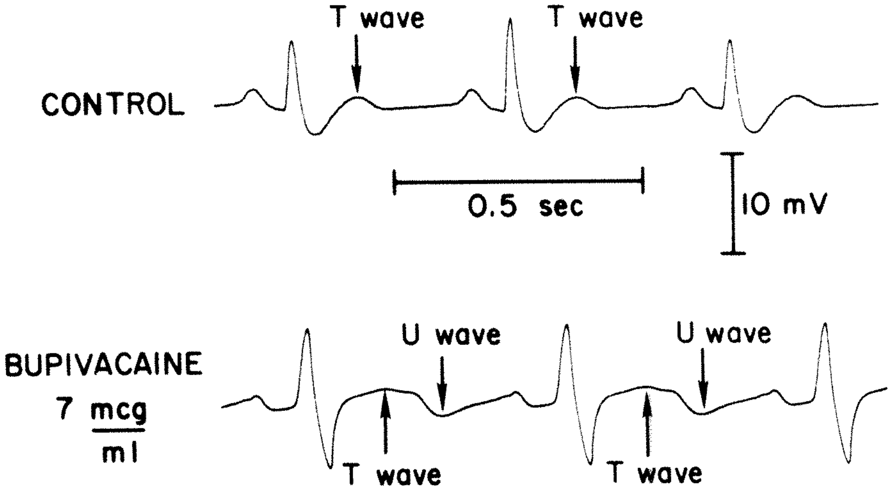


Figure 1. Bupivacaine-induced ECG alterations. Lead II surface ECG recorded at 100 mm/sec before and after bupivacaine administration. In the control period the values are: R–R interval, 0.43 sec; P–R interval, 0.10 sec; QRS duration, 0.11 sec; and Q–TU interval, 0.19 sec. Bupivacaine at a concentration of 7.0 μg/ml resulted in the following alterations: R–R interval, 0.53 sec; QRS duration, 0.12 sec; P–R interval, 0.13 sec; and Q–TU interval, 0.35 sec. The greatest change occurred in the Q–TU interval, with an increase of 84%. Note the profound repolarization changes from bupivacaine as evidenced by the appearance of the U-wave or "slow" wave after the T-wave. This was not present in the control period.

curred in all five animals given lidocaine. When compared to the bupivacaine period, in three animals the ventricular tachycardia threshold was unaltered; while in two, the threshold was actually lowered from 300 to 250 bpm after the administration of lidocaine. The differences in ventricular tachycardia threshold between the lidocaine and bretylium groups were significant. In both the bupivacaine-only and the bupivacaine-plus-lidocaine periods, the ventricular tachycardia induced was a very unusual polymorphic undulating variety as shown in Figure 2.

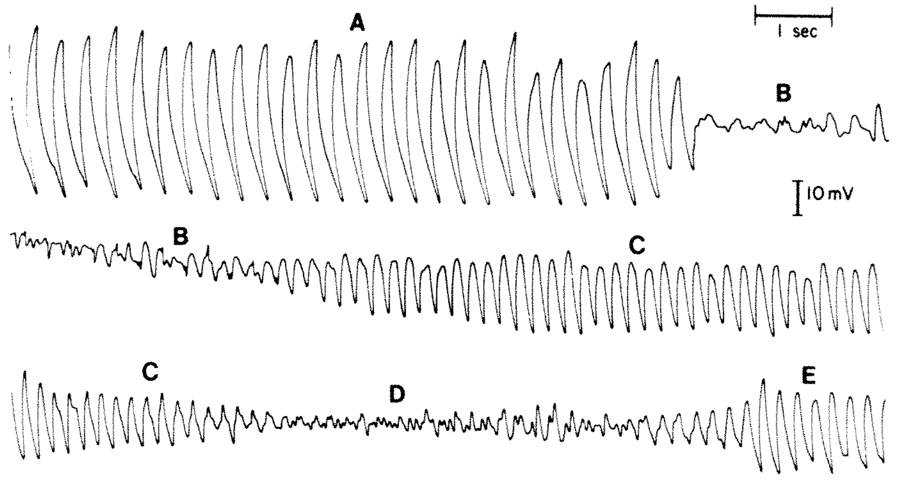
## Discussion

This study demonstrates not only the profound CV toxicity of bupivacaine but also the clear differences between lidocaine and bretylium in the treatment of these CV effects. Bupivacaine-induced alterations in cardiac output, stroke volume, heart rate, systemic vascular resistance, and mean arterial pressure were corrected with bretylium but not with lidocaine. Bupivacaine caused significant lowering of the ventricular tachycardia threshold. Bretylium consistently increased the threshold, while lidocaine was either ineffective or actually lowered the threshold even further.

Bretylium does not depress myocardial contractility directly (7). Many of the beneficial effects of bretylium can be attributed to the norepinephrine release that occurs when bretylium is taken up and concentrated in adrenergic nerve terminals (8). The high serum levels of catecholamines will increase cardiac output, stroke volume, and heart rate, thus overcoming some of the changes caused by bupivacaine. A decrease in systemic vascular resistance after bretylium either could be the result of direct vasodilation caused by the drug or a reflex vasodilation in response to increased cardiac output. In contrast, lidocaine is known to decrease cardiac output and stroke volume (9,10) at the concentrations used in this study. This is consistent with our finding that lidocaine was not helpful in restoring the alterations in cardiac output and stroke volume induced by bupivacaine.

There are several theoretical reasons for not using lidocaine to treat bupivacaine-induced arrhythmias. Lidocaine is additive with bupivacaine in lowering the seizure threshold (11). Thus it is possible for a seizure to occur when bupivacaine followed by lidocaine has been administered. Bretylium has not been reported to lower the seizure threshold (12). Lidocaine and bupivacaine both block the fast sodium channel (phase 1) in the myocardial membrane, although bupivacaine

Figure 2. Bupivacaine-induced polymorphic ventricular tachycardia. Continuous recording of lead II surface ECG at 25 mm/sec, demonstrating the unusual polymorphic undulating ventricular tachycardia occurring after stimulation of the ventricle during bupivacaine-induced Q–TU prolongation. Note that periods of "typical" ventricular tachycardia (*A* and *C*) are followed by what appears to be ventricular fibrillation (*B* and *D*), only to have "typical" ventricular tachycardia occur again (*E*). Visual inspection of the ventricle during the periods of a fibrillation-like rhythm (*B* and *D*) revealed regular organized contractions consistent with ventricular tachycardia.



differs in that the block is more profound and is rate dependent (3,13). This similar mechanism of action could explain our findings that lidocaine was not only ineffective in elevating the ventricular tachycardia threshold in all animals, but actually lowered the threshold in some. The dose of lidocaine chosen in this study was designed to produce serum levels that previously have been shown to be effective in preventing ventricular arrhythmias (14). Bretylium was given in a dose similar to that previously shown to be effective for bupivacaine ventricular arrhythmias (4).

Bretylium exerts its antiarrhythmic effects by several different mechanisms of action. Bretylium causes a marked prolongation of action potential duration in the ventricle (7,8). It also decreases the dispersion of action potential duration and effective refractory period between normal and damaged regions of the heart (15). Bretylium could terminate reentrant arrhythmias, such as ventricular tachycardia, either by its ability to prolong refractoriness without effecting propagation of cardiac impulses, or by releasing catecholamines, which would increase conduction in abnormal conducting tissues (15). Bretylium also has been shown to have a "quinidine antagonism"-like effect because it reverses some of the quinidine-induced changes in action potential duration, rate of maximal depolarization, and His–Purkinje conduction (16). Like quinidine, bupivacaine is a potent depressant of these parameters, and this bretylium antagonism may be important in treating bupivacaine arrhythmias.

None of the animals spontaneously developed any arrhythmias due to bupivacaine alone, but all underwent sustained polymorphic ventricular tachycardia upon stimulation of the ventricle. Thus it appears that bupivacaine generates conditions ripe for ventricular arrhythmias. The mechanism of ventricular arrhythmias associated with bupivacaine is not fully understood. Previous studies have shown that bupivacaine is a potent antiarrhythmic when given in low doses (0.5–1 mg/kg) intravenously (17–19). Other investigations have, as has this study, demonstrated significant conduction and repolarization changes due to bupivacaine (4,20,21). Bupivacaine causes a 50% prolongation in Q–T interval at a lower concentration than any other potent local anesthetic studied (21). The significant increase in Q–TU interval, generation of a "slow wave" following the T-wave (Fig. 1), combined with the unusual polymorphic undulating ventricular tachycardia (Fig. 2) from bupivacaine are analogous to the clinical syndrome of Torsades de Pointes (TdP).

This suggests a possible explanation for the generation of malignant ventricular arrhythmias induced by bupivacaine. Torsades de Pointes was described in 1966 by Dessertenne as a syndrome of polymorphic ventricular tachycardia occurring in the setting of Q–TU prolongation (22). Prevalent in this syndrome is an enhanced U-wave (also called a "slow-wave") following the T-wave (23,24). In TdP, the Q–TU interval prolongation can be either acquired or congenital, the acquired variety being induced by many drugs, particularly fast channel sodium blocking drugs such as procainamide, quinidine, or disopyramide (23). Bupivacaine is also a fast channel sodium blocker in the cardiac membrane that causes Q–TU interval prolongation (3,21). In TdP, the prolonged Q–TU interval allows a greater chance for an "R-on-T" phenomenon, or increased vulnerable period, and resultant malignant ventricular rhythm (23). It has also been suggested that reentry ventricular arrhythmias in TdP can result from increased dispersion of action potential duration (25). Case reports have suggested that bretylium is effective, whereas lidocaine is often not effective for the ventricular arrhythmias in TdP (23,24,26,27). Bretylium may exert its effectiveness by increasing action potential duration and increasing heart rate, effects that would tend to decrease dispersion. Other effective therapies for TdP include rapid atrial pacing and isoproterenol (23,24).

It is not clear at this time whether bupivacaine arrhythmias are a true TdP-like syndrome. Certainly there are many similarities between the two. This TdP comparison does allow an explanation of the many studies that previously have been conflicting on the differing effects of bupivacaine; especially why bupivacaine can be an antiarrhythmic in low doses but yet cause ventricular arrhythmias at higher doses (1,17–19). The most important aspect of this theory is that therapy known to be effective for TdP should be investigated as possible treatment for ventricular arrhythmias associated with potent amide local anesthetics. Isoproterenol and rapid atrial pacing would be of particular interest.

In conclusion, this study demonstrates that bretylium, but not lidocaine, is effective in reversing many of the hemodynamic and electrophysiologic effects induced by cardiovascular toxic doses of bupivacaine. The results of this study suggest that bretylium be considered an immediate treatment for ventricular arrhythmias resulting from bupivacaine. Bupivacaine may result in a TdP-like syndrome. Future studies are needed to evaluate the relationship between TdP and bupivacaine-induced arrhythmias.

The authors thank Ms. Winston Powell for invaluable technical assistance during the experiments and John Foster Fritz, MS, for editorial suggestions and manuscript revisions.

## References

1. Kotelko D, Shnider S, Dailey P, et al. Bupivacaine-induced cardiac arrhythmias in sheep. Anesthesiology 1984;60:10–8.
2. Albright G. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiology 1979;51:285–6.
3. Clarkson C, Hondeghem L, Matsubara T, Levinson G. Possible mechanism of bupivacaine toxicity: fast inactivation block with slow diastolic recovery. Anesth Analg 1984; A199.
4. Kasten GW, Martin ST. Successful resuscitation following massive bupivacaine overdose in the hypoxic dog. Anesthesiology 1984;61:A206.
5. Wellens JJ, Farre J, Brugada P, Bar FW. The method of programmed stimulation in the study of ventricular tachycardia. In: Hosephson ME, ed. Ventricular tachycardia, mechanism and management. New York: Futura, 1982;237–84.
6. Park GB, Erdtmansky PE, Brown RR, Kullbert MP, Edelson J. Analysis of mepivacaine, bupivacaine, etidocaine, lidocaine and tetracaine. J Pharm Sci 1980;69:603–5.
7. Bigger JT, Hoffman BF, Antiarrhythmic drugs. In: Gillman AG, Goodman LS, Gilman A, eds. The pharmacological basis of therapeutics. New York: Macmillan, 1980;761–92.
8. Bigger JT, Jaffe CC. The effect of bretylium tosylate on the electrophysiologic properties of ventricular muscle and purkinje fibers. Am J Cardiol 1971;27:82–92.
9. Kahn RC, Statile L, Turndorf H. Hemodynamic alterations of lidocaine at therapeutic serum concentrations. Anesthesiology 1982;57:A53.
10. Boudoulas H, Schaal SF, Lewis RP, Welch TG, DeGreen P, Kates RE. Negative inotropic effect of lidocaine in patients with coronary arterial disease and normal subjects. Chest 1977;71:170–5.
11. Munson ES, Paul WL, Embro WJ. Central nervous system toxicity of local anesthetic mixtures in monkeys. Anesthesiology 1977;46:179–83.
12. Heissenbuttel RH, Bigger JT. Bretylium tosylate: new available antiarrhythmic drug for ventricular arrhythmias. Ann Int Med 1979;91:299–38.
13. Wojtczak JA, Pratilas V, Griffin RM, Kaplan JA. Cellular mechanisms of cardiac arrhythmias induced by bupivacaine. Anesthesiology 1984;61:A37.
14. Covino BG. Perioperative management of arrhythmias. In: Kaplan JA, ed. Cardiac anesthesia, vol. 2. Cardiovascular pharmacology. New York: Grune and Stratton, 1983;395–412.
15. Cardinal R, Sasyniuk BI. Electrophysiological effects of bretylium tosylate on subendocardial purkinje fibers from infarcted canine hearts. J Pharmacol Exp Ther 1978;204:159–74.
16. DeAzeuedo IM, Watanabe Y, Dreifus LS. Electrophysiologic antagonism of quinidine and bretylium tosylate. Am J Cardiol 1974;33:633–8.
17. Boettner RB, Dunbar RW, Haley JV, Morrow DH. A comparison of the antiarrhythmic effects of bupivacaine and lidocaine. South Med J 1972;65:1328–30.
18. Dunbar R, Boettner RB, Gatz R, Pennington R, Morrow D. The effect of mepivacaine, bupivacaine, and lidocaine on digitalis induced ventricular arrhythmias. Anesth Analg 1970;49:761–6.
19. Chapin JC, Kushins LG, Munson ES, Schick LM. Lidocaine, bupivacaine, etidocaine, and epinephrine-induced arrhythmias during halothane anesthesia in dogs. Anesthesiology 1980;52:23–6.
20. Avery P, Redon D, Schaenzer G, Rusy B. The influence of serum potassium on the cerebral and cardiac toxicity of bupivacaine and lidocaine. Anesthesiology 1984;61:134–8.
21. Block A, Covino B. Effect of local anesthetic agents on cardiac conduction and contractility. Reg Anesth 1981;6:55–61.
22. Dessertenne F. La tachycardie ventriculaire a deux foyers opposes variables. Arch Mal Coeur 1966;59:263–5.
23. Smith WM, Gallagher JJ. "Les Torsades de Pointes": an unusual ventricular arrhythmia. Ann Int Med 1980;93:578–84.
24. Jackman WM, Clark M, Friday KJ, Aliot EM, Anderson J, Lazzara R. Ventricular tachyarrhythmias in the long QT syndromes. In: Zipes DP, ed. The medical clinics of North America. Philadelphia: WB Saunders, 1984;1079–109.
25. Kuo CS, Munakata K, Reddy CP, Surawicz B. Characteristics and possible mechanism of ventricular arrhythmia dependent on the dispersion of action potential duration. Circulation 1983;67:1356–61.
26. VanderArk C, Reynolds E, Kahn D, Tullett G. Quinidine syncopy. A report of successful treatment with bretylium tosylate. J Thorac Cardiovasc Surg 1976;72:464–6.
27. Redleaf PD, Lerner IJ. Thiazide-induced hypokalemia with associated major ventricular arrythmias. JAMA 1968;206:1302–4.

# Differential Spread of Blockade of Touch, Cold, and Pinprick during Spinal Anesthesia

Angelo G. Rocco, MD, Stephen A. Raymond, PhD, Ellen Murray, RN, Usha Dhingra, MD, and Dubravka Freiberger, MD

ROCCO AG, RAYMOND SA, MURRAY E, DHINGRA U, FREIBERGER D. Differential spread of blockade of touch, cold, and pinprick during spinal anesthesia. Anesth Analg 1985;64:917–23.

*The differential levels of sensory blockade of pinprick, cold, and touch were monitored throughout the course of spinal anesthesia administered to 50 patients to determine variations in the degree of spread during onset, plateau, and regression, and to establish the effects of epinephrine and the effect of posture during injection. A significant difference was observed between the dermatomal level of sensory loss of touch and the dermatomal level of loss of either pinprick or cold during onset, at 5 min in patients given tetracaine with epinephrine, at time of maximum spread in patients given tetracaine with epinephrine or in the sitting position, and in all groups during regression. Loss of touch began later, never extended as far cephalad, and regressed sooner. The extent of this difference was greatest during regression, when the anesthetic was given to patients in the sitting position, after epinephrine. The level at which the sense of touch was lost seemed to mark the limits of the zone of solid spinal anesthesia; these limits could not be assessed effectively using pinprick. We propose that loss of touch sensation be used to assess whether anesthesia is adequate to avoid tourniquet pain. If there is loss of touch sensation above the L1 dermatome, it is unlikely that tourniquet pain will occur.*

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—depth.

Anesthesiologists have been challenged by the clinical observation that pain develops from application of a tourniquet to a lower extremity in patients who have adequate levels of spinal anesthesia for orthopedic surgical procedures. There is no pain during surgery, nor are pinpricks painful in dermatomes well above the level of the surgery, yet pain from the tourniquet on the anesthetized limb occurs nonetheless in a significant number of patients (1–6). We noted in a patient with tourniquet pain that touch could be felt at the proximal margin of the tourniquet, whereas pinprick could not be felt above the umbilicus. We wondered if tourniquet pain could be related to the extent of differential sensory block during spinal anesthesia, and if so, whether this might help us to predict the occurrence of tourniquet pain.

The order in which different types of sensation are blocked during clinical spinal anesthesia was reviewed by Sinclair and Hinshaw (7), who stressed that the relative order of loss among the modalities of cold, warm, and pain is contingent upon the methods used to stimulate the patients and on the training of the patient or volunteer in sensory discrimination. However, investigators consistently have found that perception of pain, however measured, was blocked before touch. In their study on the order of loss of sensation during surgical spinal anesthesia, Heinbecker et al. (8) found that pain to pinprick was lost prior to touch (stimulus not described). In studies of differential spinal anesthesia in volunteers, Sarnoff and Arrowood (9–13) were able to produce increases in cutaneous temperature due to block of sympathetic fibers at doses of procaine that sometimes also blocked the appreciation of pinprick but spared other sensations (to light brushing and finger pressure) and voluntary motor activity. Greene's (14) interest in the differential susceptibility of the sympathetic system and the somatosensory system motivated him to compare segmental levels of anesthesia to pinprick and to cold. He used cold as an indication of probable sympathetic block believing that fibers involved in perception of cold were of equivalent susceptibility to anesthesia as the sympathetic preganglionic fibers.

---

This study was partially supported by USPHS GM30160 and GM 35647.

Received from the Department of Anesthesia, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. Accepted for publication May 1, 1985.

Address correspondence to Dr. Rocco, Department of Anesthesia, Brigham and Women's Hospital, Boston, MA 02115.

© 1985 by the International Anesthesia Research Society

Greene found that temperature discrimination failed about two spinal segments above the level corresponding to pinprick. Chambers et al. (15) have found recently that the loss of sensation to touch at 20 min after intrathecal bupivacaine was two dermatomes lower than the loss of sensation to pinprick, which has been the standard clinical tool used in evaluating the level of anesthesia.

These earlier studies have established that a differential sensory block to touch, pinprick, and cold occurs during spinal anesthesia, but they have not described the difference in dermatomal spread of block for various sensations throughout the progress of anesthesia. Nor have they compared the effects of posture, epinephrine, and different local anesthetics. Here we have tested the level of anesthesia for three types of stimulation: pinprick, touch (light pressure), and cold during spinal anesthesia.

## Materials and Methods

Patients included in this study were drawn from a population scheduled for surgery between March and June 1983. A variety of extraperitoneal procedures were done, including transurethral resection, herniorrhaphy, vein stripping, joint replacement, and other orthopedic procedures. In 10 patients a tourniquet was applied to the lower extremity to facilitate the operation. Patients were of both sexes, between 40 and 80 yr. Spinal anesthesia was administered and managed by residents in training and by staff physicians in a routine fashion for five groups. The anesthetic technique and drug were chosen on the basis of the contemplated surgery. If the patient qualified for one of the groups as detailed below, then informed consent was obtained and we made the observations. Patients were premedicated with diazepam, 5–10 mg orally, and received less than 100 μg of fentanyl in divided doses during the procedure.

The upper boundary of the loss of each sensory modality was determined by asking patients to compare the sensation when a stimulus was applied to an unanesthetized area and in the test area. The dermatome below the lowest dermatome at which the sensation was reported to feel the same as in the unanesthetized area was recorded as the upper level of loss of sensation. Tests for each modality were made every 5 min during onset, and at half-hour intervals during plateau and regression. Sensory loss of pinprick was tested using an 18-gauge sharp needle with a long bevel, of cold by touching the skin with a wet alcohol sponge and fanning with the evaluator's hand, and of touch by producing minimal tissue deformation using light pressure applied with the evaluator's finger. A chart was prepared for each patient during the course of the anesthetic, which gave the dermatomal level corresponding to the boundary of blockade of each type of stimulus at each test period. On the same record we noted occurrence of tourniquet pain, a deep, poorly localized ache. Confirmation of the presence of tourniquet pain was not actively sought; however, patients who became restless were asked if they had pain and its location. Also, we noted whether the pain disappeared with the release of the tourniquet.

Table 1. Group Characteristics

| Group | Drug | Position | Dose[a] |
|---|---|---|---|
| 1 | Tetracaine | Lateral | 11.8 ± 0.34 |
| 2 | Tetracaine with epinephrine | Lateral | 12.6 ± 0.6<br>0.23 ± 0.021 |
| 3 | Tetracaine | Sitting | 12.8 ± 0.35 |
| 4 | Tetracaine with epinephrine | Sitting | 13.5 ± 0.95<br>0.25 ± 0.02 |
| 5 | Lidocaine | Sitting | 79.1 ± 8.0 |

[a] Mean, mg ± SEM.

Fifty patients chosen sequentially were divided into the following five groups of 10 patients each, according to the anesthetic used and the patients' positions at the time of injection of local anesthetic into the subarachnoid space: tetracaine in the lateral position; tetracaine with epinephrine in the lateral position; tetracaine in the sitting position; tetracaine with epinephrine in the sitting position; and lidocaine in the sitting position. Each patient was returned to the supine position immediately after injection. The mean dose of local anesthetic and epinephrine for the ten patients in each group is summarized in Table 1. All solutions were mixed with dextrose. Statistical analysis was performed on the differences between levels for touch vs levels for pinprick or cold sensation at each sample time. Differences were considered significant if the $P$ value (1–2 $\alpha$) of the Wilcoxon test for paired samples was less than 0.05. Whenever levels for touch were compared to both levels for pinprick and levels for cold sensation, differences with $P < 0.025$ were considered significant. The $P$ values are summarized in each figure caption. For comparisons of differences between groups the unpaired $t$-test was used.

## Results

The time course of the upper segmental levels of sensory blockade of the three types of stimuli tested are given for each of the five groups in Figures 1–5.

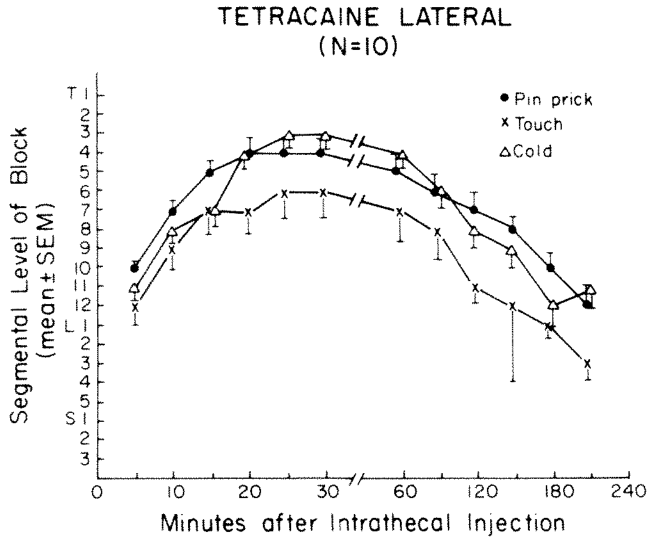


Figure 1. The upper dermatomal levels of blocks (mean ± SEM) of pinprick sensation (closed circle), touch (x), and cold sensation (open triangle) after the intrathecal administration of tetracaine with 5% dextrose to patients in the lateral position. Patients were turned supine immediately after injection. In this and all other figures the time axis was expanded during onset. After the breaks in the curves at 30 min, all subsequent samples were taken at one-half hour intervals. For touch vs pinprick, $P < 0.02$ for samples at 120, 150 and 180 min; $P < 0.05$ for samples at 15, 30, and 90 min. For touch vs cold, $P < 0.02$ for samples at 20, 25, 30, 120, and 150 min; $P < 0.05$ for samples at 60 min.

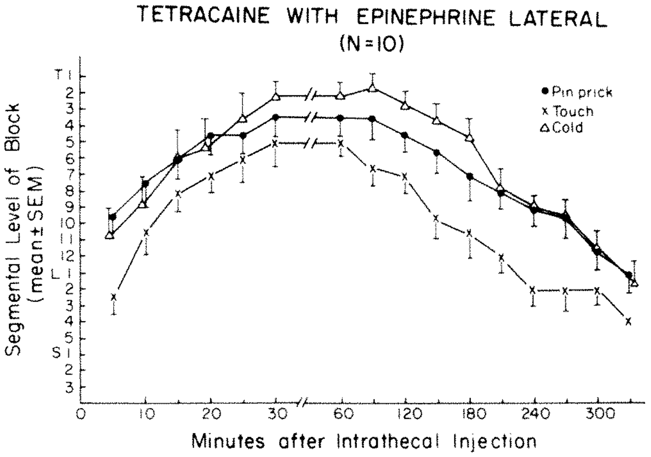


Figure 2. The upper dermatomal levels of blocks (mean ± SEM) of pinprick sensation (closed circle), touch (x), and cold sensation (open triangle) after the intrathecal administration of tetracaine with epinephrine, 0.2 mg, and 5% dextrose to patients in the lateral position. Patients were turned supine immediately after injection. For touch vs pinprick, $P < 0.02$ for all samples except at 15, 25, 30, and 300 min; $P < 0.05$ for the sample at 300 min. For touch vs cold, $P < 0.02$ for samples at 5, 60, 90, 120, 150, 180, 210, 240, and 330 min; $P < 0.05$ for samples at 10, 30 and 270 min. For pinprick vs temperature, $P < 0.05$ for samples at 60, 90, 150 and 180 min.

### *Differential Spread of Anesthetic*

It is clear from Figures 1–5 that patients in all groups could feel touch in dermatomes that were not sensitive to pinprick and cold and that the extent of the difference varied with time in the five groups.

### *The Effect of Time, Posture, and Epinephrine*

The level of loss of touch was lower than levels at which pinprick and cold sensation were blocked. At 5 min this difference was significant in the two groups given tetracaine with epinephrine. At plateau the difference for cold sensation vs touch was significant in all five groups, regardless of patient position and the presence of epinephrine. For pinprick vs touch, the difference failed to be significant only for the group given tetracaine while they were in the lateral position (Fig. 1). At regression of sensory level of pinprick to T7–T8 there was a difference in all groups. Thus the extent of the difference in level of blockade became greater during regression. Regression of the level of loss of touch to the L1–T12 dermatomal level preceded equivalent regression of levels for pinprick or cold sensation by 60 min or more.

The difference between the level of loss of touch and the level of loss of cold sensation was greatest in two conditions: the first was when the anesthetic was administered to patients in the sitting position (Fig. 1 vs 3, Fig. 2 vs 4) and the second, when epinephrine was added (Fig. 1 vs 2, Fig. 3 vs 4). Furthermore, the effect of epinephrine on the difference for touch vs either pinprick or cold sensation was enhanced when the anesthetic was given to patients in the sitting position (Fig. 1 vs 4).

It appears that when tetracaine with epinephrine was injected into patients in the lateral position, the level of block attained was about two segments higher than it was without epinephrine. On the contrary, when tetracaine with epinephrine was injected into patients in the sitting position, the level of block attained was not much changed. If anything it was somewhat lower. This suggests that the action of epinephrine in raising the level of block (18) does not occur when the anesthetic is administered to patients in the sitting position.

The differences between cold and pinprick sensation were also greater in the presence of epinephrine (Figs. 2 and 4). A difference ($P < 0.05$) of about two segments was seen at the plateau in Figure 2, with loss of sense of cold having the greatest cephalad spread. The continuity of the difference between successive test periods reinforces our impression that the level of loss of cold sensation was in fact significantly

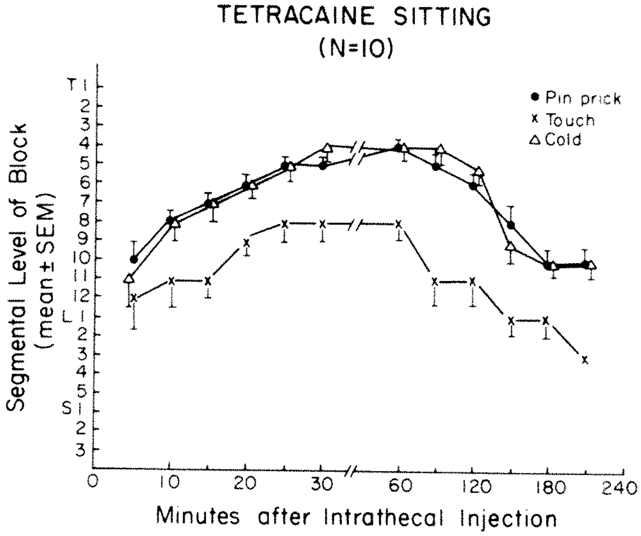


Figure 3. The upper dermatomal levels of blocks (mean ± SEM) of pinprick sensation (closed circle), touch (x), and cold sensation (open triangle) after the intrathecal administration of tetracaine with 5% dextrose to patients in the sitting position. Patients were placed supine immediately after injection. For touch vs pinprick, $P < 0.02$ for samples at 15, 20, 25, 30, 60, 90, 120 and 150 min; $P < 0.05$ at 10 min. For touch vs cold, $P < 0.02$ for samples at 15, 20, 25, 30, 60, 90, and 120 min; $P < 0.05$ for samples at 150 min.

higher than the level of loss of pinprick sensation. Our statistical analysis confirmed the significance of differences at each test period and did not take the consistency between successive periods into account.

### *Lidocaine vs Tetracaine*

Lidocaine given to patients in the sitting position was associated with results similar to those observed with tetracaine (Fig. 5 vs Fig. 3), except that the period of anesthesia was shorter for lidocaine. Also with lidocaine, the rate of regression of the level of touch appears to be greater than the rate of regression of the levels of pinprick or cold sensation. The extent of differential spread of analgesia thereby became greater with lidocaine than with tetracaine.

## Discussion

After an intrathecal injection of a local anesthetic, a concentration gradient develops with a progressive decrease in anesthetic concentration away from the site of injection (16,17). The spinal cord lies only in the cephalad limb of decreasing drug concentration. Because of differences among the spinal neural systems involved in the sensations of touch, cold, and pinprick, one would expect that sensory block of each type of stimulus would occur at differing concentrations of local anesthetics. Taken together with the orderly representation of dermatomes, the ebb and flow of the anesthetic gradient during spinal anesthesia should be accompanied by a corresponding cephalad migration and regression of the limits of sensory blockade. Only if the susceptibility to anesthetics were identical among neural systems responsible for sensory reception in the response to all three types of stimuli would the boundaries of sensory blockade on the skin increase and decrease at the same rate and pattern. Results of this study show that the boundaries of sensory blockade do not increase and decrease together, and they suggest that there is some differential sensitivity to anesthetics in the underlying neural systems.

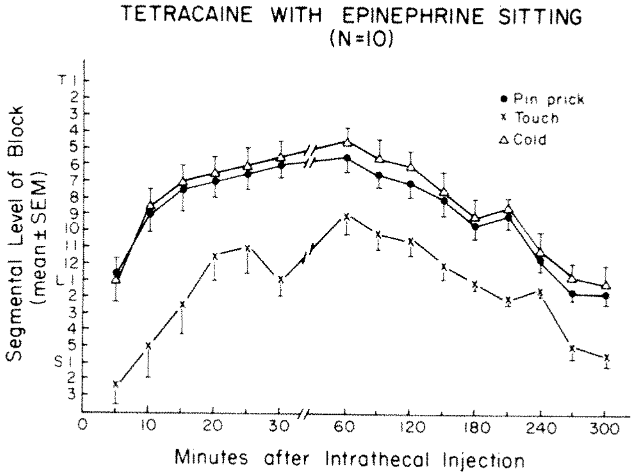


Figure 4. The upper dermatomal levels of blocks (mean ± SEM) of pinprick sensation (closed circle), touch (x), and cold sensation (open triangle) after the intrathecal administration of tetracaine with epinephrine, 0.2 mg, and 5% dextrose to patients in the sitting position. Patients were placed supine after injection. For both touch vs pinprick and cold, $P < 0.02$ for all samples except at 270 and 300 min; $P < 0.05$ for samples at 300 min.

The differential sensory blockade also may be expected to occur at the nadir of the lumbar lordotic curve when a relatively small dose of a hyperbaric solution is given to patients in the lateral position and allowed to spread with the patients in the supine position. Moore (18) found, in patients undergoing bilateral bunionectomies, after the administration of spinal block to these patients in the lateral position, that surgical anesthesia on the dependent side was satisfactory. On the contralateral side, although pinching of the skin with a forceps, taken as equivalent to pinprick, elicited no response, the patients complained of pain with incision. Thus a hyperbaric solution resulted in a differential block due to position at the time of injection.

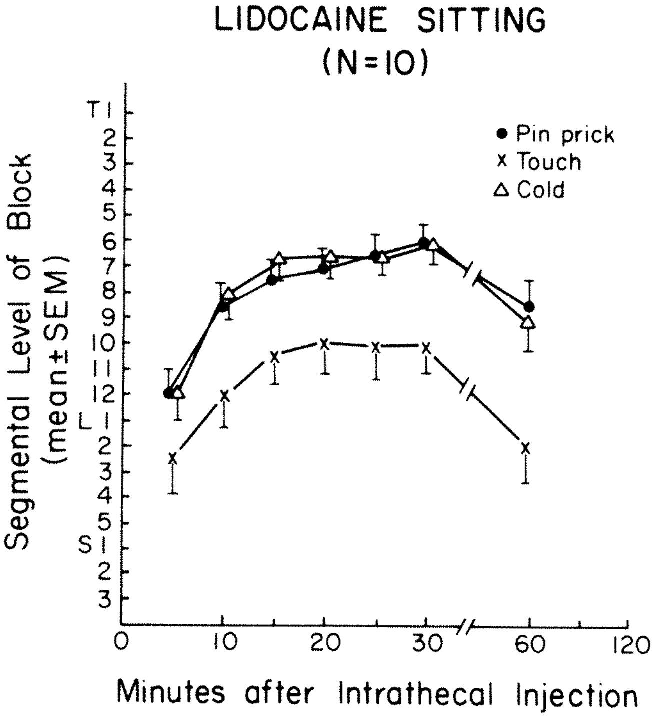


Figure 5. The upper dermatomal level of block (mean ± SEM) to pinprick sensation (closed circle), touch (x), and cold sensation (open triangle) after the intrathecal administration of lidocaine with 7.5% dextrose to a patient in the sitting position. Patient was placed supine immediately after the injection. For touch vs pinprick and cold, $P < 0.02$ for samples at 10, 15, and 60 min; $P < 0.05$ at 20 min.

Table 2. Segmental Level of Analgesia to Pinprick when Tourniquet Pain Began

| Tetracaine | Bupivacaine |
|---|---|
| $T_3$ | $T_3$ |
| $T_4$ | $T_4$ |
| $T_5$ | $L_1$ |
| $T_5$ | |
| $T_6$ | |
| $T_8$ | |
| $T_8$ | |
| $T_8$ | |
| $T_9$ | |
| $T_9$ | |
| $T_{10}$ | |
| $L_1$ | |

One patient from present study and 14 from previous studies (2,3).

### Touch vs Pinprick and Cold

Our principal result, that sensitivity to touch is more resistant in a zone of differential blockade after spinal anesthesia than sensitivity to pinprick or to cold, is consistent with prior reports (7–9,11,13).

### Utility of Multiple Stimuli

The results show that knowing the segmental level at which pinprick sensation is lost would permit one to predict the level at which the sense of cold is lost with reasonable accuracy and vice versa. Our results also show that knowing segmental levels of loss of pinprick or cold sensation will not permit prediction of the segmental level at which touch is lost. This suggests that routine use of touch with either of the other two stimuli would provide additional information to the anesthetist regarding onset and regression of anesthesia. In particular, the level of sensory block to touch would be useful in assessing the level of solid anesthesia, because touch consistently is detected well below dermatomes that are completely anesthetized to pinprick and cold sensation. The classical practice of testing patients with pinpricks, while well tolerated by most patients, occasionally does leave residual marks for a few days, particularly in older patients. The alcohol sponge seems to provide equally useful information, and we recommend a cold stimulus for routine monitoring of anesthetic level. Reproducibility and consistency of the measurements in any given patient are aided by using the method of bracketing the marginal dermatome by alternatively presenting stimuli above and below it, rather than progressing cephalad in small increments for each successive evaluation.

### Observations on Tourniquet Pain

Pain after the application of a tourniquet occurs more often without epinephrine (1). It also occurs more frequently with tetracaine than with bupivacaine (2,3). The incidence of tourniquet pain was found by Egbert and Deas (19) to depend on dose. They used two doses of tetracaine without epinephrine (12 mg and 16 mg), and there was significantly greater incidence of tourniquet pain in the group receiving the lower dose. Table 2 is a compilation of patients who developed tourniquet pain; one patient is from this study, and 14 from previous studies (2,3). As seen in this table, there is no consistent relation between segmental level of analgesia as monitored with pinprick and the occurrence of tourniquet pain. Our clinical experience is that monitoring anesthesia with pinprick alone does not permit us to predict the occurrence of tourniquet pain. The present results show a large spread between the segmental level measured with pinprick (or cold) and the level to touch, particularly during regression. As the differences in levels between touch and pinprick have become clear, we have begun to test anesthetic levels in our patients using light finger pressure (touch) and cold, as well as pinprick. Three cases will be used to present our hypothesis. In one, sensory block to pinprick extended to T10 and in the other to T3 at the time tourniquet pain occurred. The level of sensory blockade to touch, however, had descended to L2 in both these patients. In a third patient, sensory block to pinprick was found only at T12, yet the patient felt no tourniquet pain. In this patient we gave increments of anesthetic via an intrathecal catheter to maintain the level of sensory block to touch above the L2 dermatome. Thus the level of sensory block to touch appears to be the critical indicator signalling adequacy of anesthesia for tourniquet pain.

Although much research has been done on altered sensory and neurophysiologic transmission during limb ischemia, tourniquet pain remains poorly understood in three important ways. First, the site and mechanism of origin of the impulses that serve to signal the pain are unclear. This is because no reported experimental electrical recordings have been made during the patient's pain to measure discharges from nerve fibers in the peripheral nerve from the ischemic limb. Second, we know neither which fiber populations are implicated in the pain nor by what pathways impulses enter the cord. Third, the central integrative processes operating in the spinal cord during tourniquet pain are obscure. To what extent discharges in A delta and C fibers from the ischemic limb are involved in tourniquet pain is not clear, nor is it clear whether the impulses penetrate a marginal block or go around it via fibers traveling in the sympathetic trunk, as suggested by de Jong and Cullen (5).

It long has been known that repetitive activity in C fibers leads to an increased amplitude in the C elevation of the compound action potential (20). Recently, Strichartz and Zimmerman (personal communication) have shown that repetitive activity at 5–10 Hz will, in fact, penetrate a marginal anesthetic block in C fibers. In their experiments, just enough anesthetic was present to eliminate the C elevations of the compound action potential in response to single shocks. Repeated stimuli resulted in a progressive increment in the C elevation, indicating conduction past the blocked region. Repetitive activity in A fibers in marginal block in vitro, on the other hand, tends to increase block (21). Thus with impulse activity present, conduction block may increase in large A fibers, while it declines in C fibers, and this could accentuate the sensations of pain.

In summary, we find that during spinal anesthesia, sensory block to cold and pinprick sensation occurs at more cephalad dermatomes than does sensory block to touch. Touch consistently is felt in dermatomes where cold and pinprick are not felt. We also find that the zones of differential blockade are greater during the regression of spinal anesthesia and are accentuated both by the sitting position and epinephrine. Our experience suggests that loss of the sensation of touch marks the limits of the zone of solid anesthesia that could not be effectively assessed by using pinprick. This study does not resolve the mechanism of tourniquet pain. The level of sensory block to pinprick was found not to correlate with the occurrence of tourniquet pain in patients from this study and two prior studies (2,3). The difference in the regression of sensory blockade of touch and pinprick may account for this. Touch may be a better predictor of when tourniquet pain will occur.

---

This study was partially supported by USPHS GM 30160 and GM 35647. It is a pleasure to thank Dr. Philip A. Lief for comments and critical discussion, Drs. Benjamin G. Covino and Aaron Gissen for critical comments on the manuscript, and Dr. Gary R. Strichartz for his discussion of his experiments on repetitive activity in C fibers. We would also like to thank Dr. Michael Feldstein, Director of the Biostatistics Consulting Laboratory in the Department of Biostatistics, Harvard School of Public Health, for his help in choosing the method of statistical analysis.

## References

1. Concepcion M, Maddi R, Francis D, Rocco AG, Murray E, Covino BG. Vasoconstrictors in spinal anesthesia with tetracaine—a comparison of epinephrine and phenylephrine. Anesth Analg 1984;63:134–8.
2. Rocco AG, Concepcion M, Sheskey MC, Murray E, Edstrom H, Covino BG. A double-blind evaluation of intrathecal bupivacaine without glucose and a standard solution of hyperbaric tetracaine. Reg Anesth 1984;9:1–7.
3. Rocco AG, Mallampati R, Boon J, Concepcion MA, Covino BG. A double-blind evaluation of intrathecal bupivacaine and tetracaine. Reg Anesth 1984;9:183–7.
4. Cole F. Tourniquet pain. Anesth Analg 1952;31:63–4.
5. de Jong RH, Cullen SC. Theoretical aspects of pain: bizarre pain phenomena during low spinal anesthesia. Anesthesiology 1963;24:628–35.
6. Greene NM. Physiology of spinal anesthesia. Baltimore: Williams and Wilkins, 3rd ed. 1981:36–7.
7. Sinclair DC, Hinshaw JR. Sensory changes in procaine nerve block. Brain 1950;73:224–43.
8. Heinbecker P, Bishop GH, O'Leary J. Analysis of sensation in terms of nerve impulses. Arch Neurol Psychiat 1934;31:34–53.
9. Sarnoff SJ, Arrowood JG. Differential spinal block. A preliminary report. Surgery 1946;20:150–9.
10. Sarnoff SJ, Arrowood JG. Differential spinal block II. The reaction of sudomotor and vasomotor fibers. J Clin Invest 1947;26:203–16.
11. Sarnoff SJ, Arrowood JG. Differential spinal block III. The block of cutaneous and stretch reflexes in the presence of unimpaired position sense. J Neurophysiol 1947;10:205–10.
12. Arrowood JG, Sarnoff SJ. Differential spinal block. V. Use in

the investigation of pain following amputation. Anesthesiology 1948;9:614–22.

13. Arrowood JG. Differential spinal block with particular reference to hypertensive patients. Proc Roy Soc Med 1950;43:919–28.
14. Greene NM. Area of differential block in spinal anesthesia with hyperbaric tetracaine. Anesthesiology 1958;19:45–50.
15. Chambers WA, Littlewood DG, Edstrom HH, Scott DB. Spinal anaesthesia with hyperbaric bupivacaine: effects of concentration and volume administered. Br J Anaesth 1982;54:75–9.
16. Helrich M, Papper EM, Brodie BB, Fink M, Rovenstine EA. The fate of intrathecal procaine and the spinal fluid level required for surgical anesthesia. J Pharmacol Exp Ther 1950;100:78–82.
17. Kitahara T, Kuri S, Yashida S. Spread of drugs used for spinal anesthesia. Anesthesiology 1956;17:205–8.
18. Moore DC. Factors influencing spinal anesthesia. Reg Anesth 1982;7(1):20–5.
19. Egbert LD, Deas TC. Cause of pain from a pneumatic tourniquet during spinal anesthesia. Anesthesiology 1962;23:287–90.
20. Douglas WW, Ritchie JM. Mammalian nonmyelinated nerve fibers. Physiol Rev 1962;42:297–334.
21. Courtney KR, Kendig JL, Cohen EN. Frequency-dependent conduction block. Anesthesiology 1978;48:111–17.

ANESTH ANALG
1985;64:924–8

# Hemodynamic and Plasma Catecholamine Responses to Epinephrine-Containing Perianal Lidocaine Anesthesia

W. Byron Barber, MD, Lee E. Smith, MD, Gary P. Zaloga, MD,
J. Raymond Fletcher, MD, PhD, David Cook, MD, C. Raymond Lake, MD, PhD,
and Bart Chernow, MD, FACP

BARBER WB, SMITH LE, ZALOGA GP, FLETCHER JR, COOK D, LAKE CR, CHERNOW B. Hemodynamic and plasma catecholamine responses to epinephrine-containing perianal lidocaine anesthesia. Anesth Analg 1985;64: 924-8.

*Despite the frequent use of large volumes (30–40 ml) of epinephrine-containing local anesthetic solutions for ano–rectal surgery, little is known about the anesthetic-induced hemodynamic consequences. Therefore, we measured the heart rate, blood pressure, and plasma catecholamine (norepinephrine and epinephrine) responses to the perianal injection of 40 ml of 0.5% lidocaine alone (n = 8) or 0.5% lidocaine with 1:200,000 epinephrine (n = 10) in 18 healthy adults undergoing outpatient ano–rectal surgery. The mean ± SEM plasma epinephrine concentration increased from a baseline of 42 ± 7 pg/ml to a peak of 622 ± 94 pg/ml 4 min after injection of epinephrine-containing anesthetic (P < 0.001), whereas lidocaine alone increased the mean plasma value from 36 ± 9 pg/ml (baseline) to only 69 ± 16 pg/ml (not significantly different) at its peak. Despite the increases in plasma epinephrine levels in the group receiving epinephrine-containing anesthesia, no changes in blood pressure, heart rate, or plasma norepinephrine levels were observed. Given the advantages (including prolongation of the duration of anesthesia) of adding epinephrine to perianal local anesthetics, our data support its safe use in healthy adults.*

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—infiltration. ANESTHETICS, LOCAL—lidocaine blood levels. SYMPATHETIC NERVOUS SYSTEM—epinephrine.

Epinephrine-containing local anesthetics are widely used because epinephrine (EPI) delays the absorption of lidocaine into the circulation, thereby prolonging the duration of anesthesia (1,2). For ano–rectal surgery, large volumes (40 ml) of local anesthetic are often required to achieve adequate anesthesia. The potential deleterious hemodynamic effects of EPI absorbed from these large volumes of anesthetic solutions (given in the ano–rectal area) are unknown.

In their classic review article on the interaction between anesthetic agents and adrenergic drugs, Katz and Epstein (3) recommend that normal adults receive no more than 10 ml of 1:100,000 EPI subcutaneously during halothane, cyclopropane, and trichlorethylene anesthesia, to avoid cardiac arrhythmias. EPI given subcutaneously also increases systolic blood pressure (BP) and heart rate (HR), decreases diastolic BP, and increases the cardiac work load (4). Prior studies (5–7) of the hemodynamic changes associated with infiltration anesthesia have involved much smaller anesthetic volumes (e.g., 1.8 ml for dental anesthesia) than those required for ano–rectal surgery. At our hospital, ano–rectal procedures are performed almost exclusively under local anesthesia using 40 ml of 0.5% lidocaine with 1:200,000 EPI injected into the submucosa of the rectum and anus. The amount of EPI in this volume available for absorption is 0.2 mg, the maximum dosage that can be given safely to an adult cardiac patient (8) and up to 11 times the amount used

---

The opinions expressed herein are those of the authors and are not to be construed as reflecting the views of the Navy Department, of the Naval Service at large or of the Department of Defense.

Portions of this work were supported in part by project CIP #82-06-1751 and Research Task Number M0095.001.1032 from the Bureau of Medicine and Surgery, Navy Department, Washington, DC.

Received from the Department of Surgery, George Washington University Medical Center, Washington, DC; the Departments of Surgery, Critical Care Medicine, and Internal Medicine, Endocrinology-Metabolism Branch, Naval Hospital, Bethesda; the Naval Medical Research Institute; and the Departments of Medicine, Surgery, Pharmacology and Psychiatry, Uniformed Services University of the Health Sciences, Bethesda, Maryland. Accepted for publication April 4, 1985.

Address correspondence to Dr. Chernow, Box #123, Naval Hospital, Bethesda, MD 20814-5011.

© 1985 by the International Anesthesia Research Society

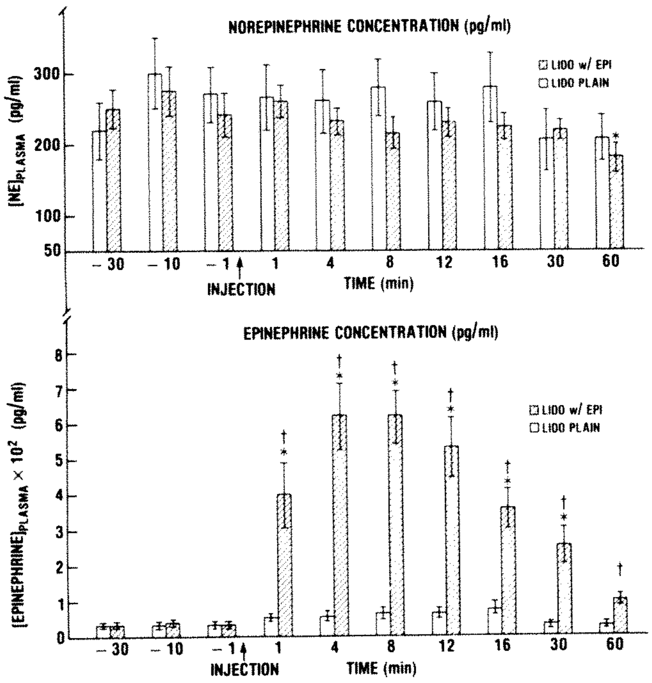


Figure 1. Mean ± SEM plasma epinephrine and norepinephrine levels at three baseline points (−30, −10, −1 min) before and after injection (arrow) of 40 ml of 0.5% lidocaine with (hatched bars) or without (open bars) 1:200,000 epinephrine. The −10 point represents the baseline value against which all other values are compared for statistical significance. Asterisk (*) indicates a significant difference between a given value and baseline. Cross (+) indicates a significant difference between paired values at a given time point.

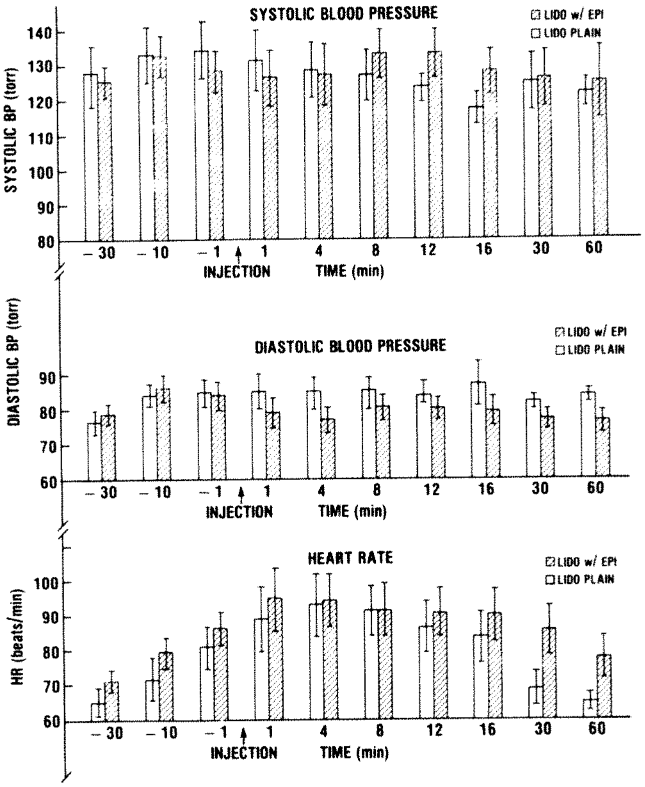


Figure 2. Mean ± SEM systolic and diastolic BP, heart rate, at three baseline points (−30, −10, −1 min) and after injection (arrow) of 40 ml of 0.5% lidocaine either with (hatched bars) or without (open bars) epinephrine.

for dental patients (5–7). The present study was designed to measure the hemodynamic and plasma EPI and norepinephrine (NE) responses to the administration of local ano–rectal anesthesia.

## Materials and Methods

Eighteen patients (four women and 14 men, mean age of 47 yr, range 28–75 yr) were studied in a protocol approved by our hospital's institutional review board. Patients fasted overnight and refrained from cigarette smoking prior to their surgical procedure. All patients scheduled for hemorrhoidectomy ($n = 6$) were given ano–rectal anesthesia with lidocaine containing EPI because of the necessity for providing a dry surgical field. This eliminated our ability to have a blinded randomized protocol. Patients scheduled for other ano–rectal operations (lateral sphincterotomy, fistulectomy/fistulotomy, and excision of anal condyloma, $n = 12$) were randomized so that four would receive 40 ml 0.5% lidocaine with 1:200,000 EPI and eight would receive anesthesia with 40 ml 0.5% lidocaine without EPI ($n = 10$ for lidocaine and EPI group, $n = 8$ for lidocaine alone). Randomization was done by using a random number table for the first eight patients undergoing other ano–rectal surgery.

### *Experimental Protocol*

With the patient in a supine position, an 18-gauge catheter was inserted into an antecubital vein and attached to a three-way stopcock for blood sampling. Blood pressure was measured in the contralateral arm by auscultation, using a sphygmomanometer, while HR was continuously monitored using a Hewlett-Packard 7834A cardiac monitor.

Twenty minutes after intravenous catheter insertion, the first blood sample for plasma catecholamine assays was drawn and the baseline HR and BP recorded. The patient was then placed in a knee–chest position for 10 min before any manipulations were made. During this period a second baseline blood sample was collected, and hemodynamic parameters were again measured. These baseline variables were used to calculate the statistical significance of all subsequent data. (Baseline is recorded as the −10 time point in Figures 1 and 2.) Diazepam (10 mg) and meperidine (50–100 mg, dosage adjusted for age, weight,

Table 1. Hemodynamic and Plasma Catecholamine Responses to Local Ano–rectal Anesthesia

| | Lidocaine with epinephrine group ($n$ = 10) | | | | Lidocaine alone group ($n$ = 8) | | | |
|---|---|---|---|---|---|---|---|---|
| | Baseline ± SEM[a] | Peak value[a,b] | Time (min) of peak mean value[c] | $P$ value[d] | Baseline ± SEM[a] | Peak mean value[b] | Time (min) of peak mean value[c] | $P$ value[d] |
| HR (beats/min) | 80 ± 4 | 95 ± 9 | 4 | NS | 72 ± 6 | 93 ± 9 | 4 | NS |
| Systolic BP (torr) | 130 ± 6 | 133 ± 7 | —[e] | NS | 133 ± 8 | 134 ± 8 | —[e] | NS |
| Diastolic BP (torr) | 86 ± 4 | 76 ± 3 | 60 | NS | 84 ± 3 | 82 ± 2 | —[e] | NS |
| EPI (pg/ml) | 42 ± 7 | 622 ± 94 | 8 | <0.001 | 36 ± 9 | 69 ± 16 | 16 | NS |
| NE (pg/ml) | 277 ± 32 | 183 ± 22 | 60 | <0.05 | 297 ± 52 | 206 ± 39 | 30 | NS |

[a] Baseline value ± SEM obtained 10 min before anesthetic injection.
[b] Value ± SEM representing the greatest value above or below the baseline.
[c] Number of min after injection of anesthetic at which the greatest change over baseline was obtained.
[d] Statistical significance of the peak value as compared to baseline value.
[e] Blanks indicate that the observed values at the different time points were essentially the same, such that no rise was enough to qualify as a peak value.

and clinical response of the patient) were given intravenously to provide sedation and analgesia, respectively. Five minutes after these medications were given, another blood sample was drawn and the BP and HR recorded. Immediately thereafter, 2–3 ml of local anesthesia was injected into the perianal skin in a circumferential manner. A 22-gauge spinal needle was next used to inject the remainder of the 40 ml of anesthetic solution into the submucosa of the rectum and anus in eight different sectors around the anal canal. An aspirating technique was used to prevent intravenous injection. The surgeon's index finger was inserted into the rectum to help direct the spinal needle to the correct depth during the injection. Approximately 4–5 ml of anesthetic was injected into each location so that the total volume of anesthetic in each patient was always 40 ml. Blood samples were drawn, and hemodynamic measurements were made 1, 4, 8, 12, 16, 30, and 60 min after completion of the anesthetic administration. The operation was begun precisely 12 min after completion of the injection of the anesthetic.

### *Catecholamine Assay and Blood Collection*

Each blood sample was placed into a 12-ml chilled, heparinized, glass test tube that was immediately placed in wet ice for approximately 10 min before being centrifuged at 3000 RPM for 10 min at 4°C. The plasma was then separated and placed into glutathione-containing plastic test tubes that were stored at −70°C until assayed. Assay of plasma NE and EPI concentrations was done by a radioenzymatic technique in which a partially purified enzyme, catechol-o-methyl transferase (COMT), catalyzes the transfer of a $^3$H-methyl group from commercially available $^3$H-S-adenosylmethionine to the meta-hydroxyl group of endogenous NE and EPI, forming $^3$H-normetanephrine and $^3$H-metanephrine, respectively. Measurements are accurate to levels of 15 pg of NE or EPI per ml of plasma (8).

### *Data Analysis*

Data were analyzed by the two-tailed paired Student's $t$-test and by analysis of variance. Results are expressed as mean ± SEM. To minimize the effect of inflating the $\alpha$ level with our use of multiple hypothesis tests, we have chosen to label as significant only those $P$ values less than 0.005.

## Results

Baseline values for systolic and diastolic BP, HR, and plasma EPI and NE concentrations were similar in the two groups (Figs. 1,2; Table 1). The mean (± SEM) plasma EPI concentration in the group of patients receiving lidocaine with EPI began to increase significantly ($P < 0.001$) above baseline levels (42 ± 7 pg/ml) at 1 min after anesthetic injection and peaked between 4 min (622 ± 94 pg/ml) and 8 min (620 ± 75 pg/ml) (Fig. 1, Table 1). The mean plasma EPI level in the "lidocaine only" group did not change (Fig. 1, Table 1). No anesthetic-induced changes in plasma NE were observed (Fig. 1, Table 1).

Systolic and diastolic BP and HR did not change significantly during the study in either group. No ECG abnormalities occurred in any of the 18 patients during the study.

## Discussion

The addition of a vasoconstrictor such as EPI to a local anesthetic solution to be used in the highly vascular ano–rectal area is important in the successful performance of ano–rectal surgical procedures (2). Previous studies investigating the hemodynamic effects of an exogenous source of EPI (5–7) have not employed the large volume of anesthetic agent commonly used in the ano–rectal surgery. In the present study we addressed the safety of utilizing 40 ml of lidocaine with EPI by measuring the plasma catecholamine and hemodynamic responses to such ano–rectal local anesthesia.

In patients receiving lidocaine with EPI, there was an anesthetic-induced increase in the plasma EPI concentration 15-fold above baseline levels. Furthermore, the EPI concentration remained elevated throughout the entire procedure. The plasma EPI level 60 min after injection was twice the baseline level. In patients given lidocaine without EPI, no significant change in the plasma EPI level was noted at any time during the procedure (Fig. 1). This indicates that the high plasma EPI levels noted in the "EPI group" are exogenous in origin and not secondary to the stress of the procedure. The NE levels remained essentially unchanged in both groups (Fig. 1), confirming previous reports on the use of EPI-containing local anesthesia (6,7).

Despite a 15-fold increase in the plasma EPI concentration after the injection of lidocaine with EPI, hemodynamic responses were negligible. Threshold levels of plasma EPI at which certain hemodynamic changes can be expected have been studied by Clutter et al. (9,10) who reported that HR increases at plasma EPI levels of about 100 pg/ml. Our mean EPI values were six times higher than these levels, and yet no clinically important or statistically significant increases in HR were observed, although all patients in both groups exhibited a tendency toward a higher HR. Clutter et al. reported increased systolic BP with plasma EPI values greater than 125 pg/ml and decreased diastolic BP with EPI values exceeding 200 pg/ml. None of these changes were noted in our study, despite plasma EPI values higher than reported by Clutter et al.

Several observations can be made regarding differences between the studies of Clutter et al. and the present work. First, EPI was injected subcutaneously in our patients, intravenously in those of Clutter et al. In spite of this difference, other investigators report similar hemodynamic effects from subcutaneous and intravenous EPI (4). Second, the mean age of our patients was 47 years, an older population than theirs, who had an average age of 28 years. We do not know if younger patients have a greater hemodynamic response to EPI than older patients. Third, patients in the present study were given intravenous meperidine and diazepam. Both of these drugs can cause hypotension (11,12) and may therefore lessen the observed cardiovascular response to EPI. Fourth, the amount of lidocaine (200 mg) given to patients in this study may have resulted in plasma lidocaine blood levels between 0.5 and 3.5 μg/ml (13–15). Lidocaine blood levels ranging from 0.6–2.0 μg/ml have been reported as concentrations necessary to treat or prevent ventricular irritability after myocardial infarction (15). The addition of lidocaine to EPI has been shown to increase by a factor of two the maximum safe submucosal dose of EPI for inducing ventricular irritability after halothane anesthesia (16). Thus the blood levels of lidocaine may have modified the cardiovascular responses to the blood levels of EPI observed in our patients in the same way that lidocaine protects against epinephrine-induced arrhythmias (16–18).

The authors would like to thank Dominic S. D'Angona, JR, for his technical assistance and David F. Cruess, PhD for his advice on our statistics.

## References

1. Braun H. Die Lokalanastesie, ihre wirsenschaftlichen Grundlagen und die praktische Anwendung. Vierte Auflage, Verlag von Johann Ambrosius Barth, Leipzig, 1914.
2. Aberg G. Studies on the duration of local anesthesia: a possible mechanism for the prolonging effect of "vasoconstrictors" on the duration of infiltration anesthesia. Int J Oral Surg 1980;9:144–7.
3. Katz RL, Epstein RA. The interaction of anesthetic agents and adrenergic drugs to produce cardiac arrhythmias. Anesthesiology 1968;29:763–84.
4. Weiner N. Norepinephrine, epinephrine and the sympathomimetic amines. In: Gilman AG, Goodman S, Gilman A eds. The pharmacological basis of therapeutics, 6th ed. New York: Macmillan, 1980:138–75.
5. Piperno S, Kaim J. Epinephrine in local anesthesia—effect on the blood pressure of normotensive patients. NYS Dent J 1981;47:392–4.
6. Tolas AG, Pflug AE, Halter JB. Arterial plasma epinephrine concentrations and hemodynamic responses after dental injection of local anesthetic with epinephrine. J Am Dent Asso 1982;104:41–3.
7. Chernow B, Balestrieri F, Ferguson CD, et al. Local dental anesthesia with epinephrine: minimal effects on the sympathetic nervous system or on hemodynamic variables. Arch Intern Med 1983;143:2141–3.
8. Durrett LR, Ziegler MG. A sensitive radioenzymatic assay for catechol drugs. J Neurosci Res 1980;5:587–98.
9. Clutter WE, Bier DM, Shah SD, et al. Epinephrine plasma metabolic clearance rates and physiologic thresholds for metabolic and hemodynamic actions in man. J Clin Invest 1980;66:94–101.
10. Clutter WE, Cryer PE. Plasma dose–response studies with noradrenaline and adrenaline in man. Prog Biochem Pharmacol 1980;17:84–9.
11. Baldessarini RJ. Drugs and the treatment of psychiatric disorders. In: Gilman AG, Goodman LS, Gilman A eds. The pharmacological basis of therapeutics. 6th ed. 1980:437–47.
12. Jaffe JH, Martin WR. Opioid analgesics and antagonists. In: Gilman AG, Goodman LS, Gilman A, eds. The pharmacological basis of therapeutics. 6th ed. New York: Macmillan 1980:513–8.

13. Harrison DC. Practical guidelines for the use of lidocaine. Prevention and treatment of cardiac arrhythmias. JAMA 1975;233:1202–4.
14. Zito RA, Reid PR, Longstreth JA. Variability of early lidocaine levels in patients. Am Heart J 1977;94:292–296.
15. Stoelting RK. Plasma lidocaine concentrations following subcutaneous or submucosal epinephrine–lidocaine injection. Anesth Analg 1978;57:724–6.
16. Johnston RR, Eger EI, Wilson C. A comparative interaction of epinephrine with enflurane, isoflurane and halothane in man. Anesth Analg 1976;55:709–12.
17. Katz RL. Interaction of epinephrine. Anesth Analg 1977;56:747.
18. Horrigan RW, Eger EI, Wilson C. Epinephrine-induced arrhythmias during enflurane anesthesia in man: a nonlinear dose-response relationship and dose-dependent protection from lidocaine. Anesth Analg 1978;57:547–50.

ANESTH ANALG
1985;64:929–32

# Morphine Concentration in Brain and Spinal Cord after Subarachnoid Morphine Injection in Baboons

M. A. Gregory, MSC, J. G. Brock-Utne, MD, FFA, S. Bux, BSC, and
J. W. Downing, MBBCH, FFARCS

GREGORY MA, BROCK-UTNE JG, BUX S, DOWNING JW. Morphine concentration in brain and spinal cord after subarachnoid morphine injection in baboons. Anesth Analg 1985;64:929–32.

*Tritium-labeled morphine was injected into the lumbar (L4–5) subarachnoid space of three baboons. The animals were sacrificed 3, 6, and 24 hr thereafter. Morphine concentrations were measured at five predetermined positions within the spinal cord, medulla oblongata, and frontal lobes of the brain by scintillation-count assay. The results revealed that morphine ascends in the subarachnoid space and is absorbed into the spinal cord and medulla oblongata in a time-dependent fashion. Ventilation was most depressed and maximal concentrations of morphine were detected in the medulla six hours after injection. Delayed respiratory depression, occasionally reported after intraspinal morphine injection, may therefore be caused as a result of the affinity of morphine for binding sites, possibly opiate receptors, situated within the vital respiratory and cardiovascular neuronal complexes of the medulla.*

Key Words: ANESTHETIC TECHNIQUES, SPINAL—morphine. ANALGESICS, MORPHINE—spinal.

Pain relief by either epidural or intrathecal opioid injection has proved successful in clinical practice. However, factors that influence the cerebrospinal fluid (CSF) pharmacokinetics of these drugs after intraspinal injection remain poorly understood. The life-threatening ventilatory depression described several hours after intraspinal morphine injection has caused concern as to the safety of this technique (1–3).

With few exceptions (4,5), most investigations into the physiologic responses to and pharmacokinetics of intrathecally injected drugs have been limited to studies in nonprimates (6,7). In an attempt to better understand the CSF pharmacokinetics of intraspinal morphine in primates, we injected tritium-labeled morphine subarachnoidally into baboons and examined its subsequent localization in the spinal cord and medulla oblongata.

## Methods

One male and two female adult baboons (*Papio ursinus*) of mean weight 22.7 kg (range 19–27 kg) were studied. The animals were anesthetized with intramuscular ketamine (10–20 mg/kg). Thereafter, to maintain anesthesia during the study period, ketamine was administered intravenously in bolus doses of 1 mg/kg when required. Prior to intrathecal injection, the lumbar region (L4–5) of each baboon was closely shaved and cleaned. Using a Terumo 22-g spinal needle, 1 ml of isotonic saline containing 1 millicurie of H morphine (2.5 mg/ml—Amersham International, UK) was injected into the subarachnoid space of each animal (L4–5). Thereafter, all intrathecal injections were performed with the animal in the right lateral position. The animals were left in the supine position for the duration of the study. At 3 (baboon 1), 6 (baboon 2) and 24 (baboon 3) hr after the subarachnoid injection, while still anesthetized, the animals were sacrificed by injections of concentrated potassium chloride solution in the heart. At autopsy, performed within minutes of death, the entire spinal cord, medulla and brain were carefully removed. The cord was severed above the medulla and quenched in liquid nitrogen to facilitate retention of shape during the biopsy procedures. A block of the frozen tissue was taken from the site of injection and the medulla oblongata in each animal. Using the injection site as a marker, we obtained additional blocks of tissue from 5 cm below and 5, 10, and 20 cm above this site. In addition, to serve as $^3$H negative controls, tissue from the frontal lobes of each brain was quenched and prepared for cryosectioning.

---

Received from the Departments of Physiology and Anaesthetics, University of Natal Medical School, Durban, Republic of South Africa. Accepted for publication April 12, 1985.

Address correspondence to Dr. Brock-Utne, Department of Physiology, Faculty of Medicine, University of Natal, PO Box 17039, Congella 4013, Natal, Republic of South Africa.

© 1985 by the International Anesthesia Research Society

### *Cryosectioning, Tissue Solubilizing, and Scintillation Counting Procedures*

Using a Reichert Frigocut cryostat at a chamber temperature of −15°C, cryosections of 20 $\mu$m were made of the brain, medulla oblongata, and each of the transversely orientated blocks of spinal cord. Four pairs of sections were cut from each block. Each pair of sections was immersed in 1 ml of Soluene 350 (Packard) solubilizing solution in four scintillator vials (2 × 20 $\mu$m sections × 4 vials/block). In addition, sections of each block were mounted on glass slides, fixed in Bakers fluid, and stained with hematoxylin and eosin (H & E) for light microscopy. After solubilization for 24 hr at 22°C, the resultant solution was reconstituted to 10 ml with Insta-Gel scintillation fluid (Packard). To reduce chemiluminescence, the solution was stabilized for 24 hr at 22°C in the dark. Insta-Gel solutions with and without 1 ml of Soluene were prepared to serve as background controls. Using a Packard Tri-Carb liquid scintillation counter (model 3380), 10-min counts were made of each vial.

### *Compensating Specimen Count for Tissue Volume*

The cross-sectional areas of individual specimens of spinal cord, medulla, and brain varied extensively within and between animals. To compensate for such variations and to enable morphine concentrations within specimens to be quantified, the following methods were employed.

The transverse area of individual specimens was determined from H & E cryosections by means of a VIDS 'System 111' semiautomatic image analyzer. Utilizing all available data, a formula was constructed that compensated specimen counts per minute (CPM) for tissue volume variations:

$$\frac{\text{Specimen CPM}}{\text{Section area (mm}^2) \times \text{thickness } (4 \times 10^4)} = \text{CPM/mm}^3 \text{ of tissue.}$$

## Results

Six hours after the administration of tritiated morphine, the respiratory rate of baboon 2 had slowed from 17 to 9 breaths/min and baboon 3 from 16 to 8 breaths/min. In baboon 1, no clinically significant change in respiratory rate was noted. In baboon 3, ventilatory depression lasted for approximately 1 hr, after which the respiratory rate slowly increased to normal over a further period of 2 hr.

Table 1 and Figure 1 summarize the data in terms of mean CPM/mm$^2$ of tissue for each position minus the mean background CPM. Three hr after injection, high concentrations of morphine were detected in the immediate vicinity of the injection site. Six hr after injection, substantial levels of morphine were detected over the length of the cord and medulla oblongata. At 24 hr after injection, no morphine could be detected other than a small concentration in the immediate vicinity of the injection site. Note that $^3$H levels in control brain tissue were within scintillator/soluene fluid limits.

Table 1.

| Baboon | Time | Counts per minute ($\times 10^4$)/mm$^3$ of tissue | | | | | | |
|---|---|---|---|---|---|---|---|---|
| number | (hr) | Pos.1 | Pos.2 | Pos.3 | Pos.4 | Pos.5 | Pos.6 | Pos.7 |
| 1 | 3 | 118 | 125 | 49 | 7.5 | 1.9 | 0.09 | 0.05 |
| 2 | 6 | 44 | 46 | 41 | 16.0 | 9.6 | 7.2 | — |
| 3 | 24 | 12 | 15 | 4 | 0.1 | 0.04 | 0.03 | — |

Abbreviations: Pos.1, 5 cm below injection site; Pos.2, injection site; Pos.3, 5 cm above injection site; Pos.4, 10 cm above injection site; Pos.5, 20 cm above injection site; Pos.6, pons medulla; Pos.7, frontal lobe. All CPM have had background CPM deducted. Bab. No., Baboon identification (see Methods). Time, Time of sacrifice after subarachnoid morphine injection.

## Discussion

Respiratory depression after both intrathecal and extradural morphine may be immediate or delayed. Immediate depression, thought to be caused by the rapid systemic absorption of morphine, is easily diagnosed and therefore easily managed. Delayed respiratory depression often proves a more serious condition, especially if monitoring of patients is inadequate. In humans, delayed respiratory depression has been observed most frequently 10 hr after intrathecal morphine injection, with attenuated ventilatory response recorded up to 22 hr after the epidural administration of this drug (3,8).

Delayed respiratory depression is thought to be caused by the rostral spread of morphine in the CSF (3,9). Helrich et al. (9) found that procaine ascends the subarachnoid space in a time-dependent fashion. Our observations suggest that morphine ascends in a similar manner. For 3 hr after injection, morphine was particularly concentrated in the immediate vicinity of the injection site, whereas 6 hr after injection there was a much more even distribution of morphine over the length of the cord and medulla (Table 1, Fig. 1). During the course of this study, however, no significant levels of morphine were detected in the frontal lobes.

The mechanisms involved in eliminating drugs from the CSF were not investigated as part of this study. It is interesting to note, however, that in this study,

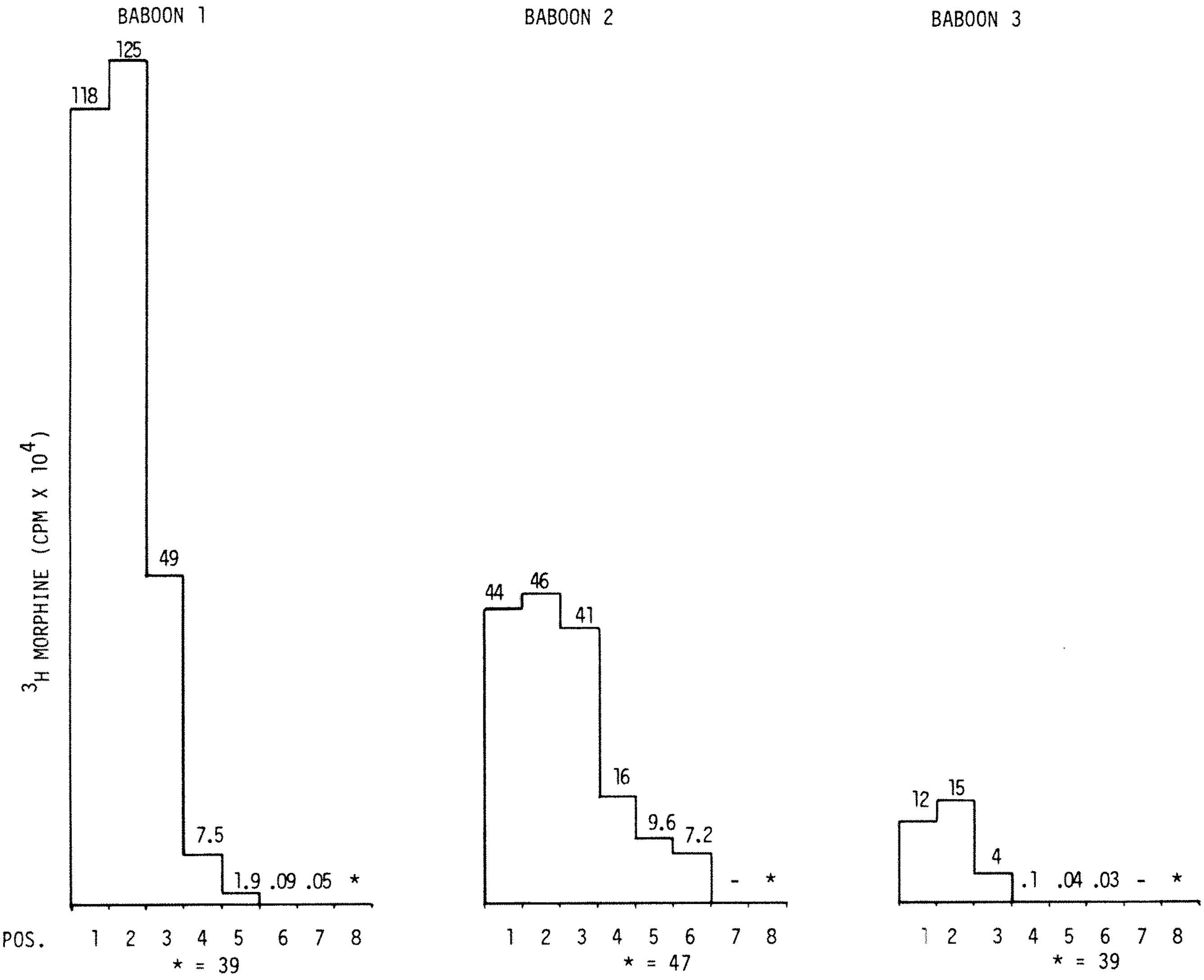


Figure 1. Histograms showing the positional distribution of $^3H$ in baboon spinal cords 3 hr (Baboon 1); 6 hr (Baboon 2), and 24 hr (Baboon 3) after the intrathecal injection of $^3H$ morphine. For key to positions (Pos.) 1–7, see Table 1. Pos. 8 (*), background CPM.

morphine elimination is almost complete 24 hr after intrathecal injection.

In clinical practice, after intrathecal injection of morphine, the onset of respiratory depression may vary quite considerably. In this study, baboon 2 and 3 showed some respiratory depression 6 hr after morphine injection. The presence of moderately high concentrations of morphine in the medulla at this time suggested a relationship between these two phenomena. The medulla oblongata, a region rich in opiate receptors, is situated dangerously close to vital respiratory and cardiovascular centers. It is proposed that by its binding with opiate receptors in this region, morphine is responsible for the observed delayed respiratory depression.

This study indicates that morphine ascends the subarachnoid space and binds to receptors, possibly opiate, in the spinal cord and cerebellum in a time-dependent fashion. Drug concentration appears to vary inversely with distance from site of injection. It is suggested that delayed respiratory depression after subarachnoid and epidural morphine injection is caused as a result of the affinity of morphine for binding sites near the respiratory neuronal complexes of the medulla oblongata. We therefore concur with Bromage (1) that unless special surveillance is provided, the single-bedded hospital room with all its comforts and privacy is not a safe place because of the risk of delayed respiratory depression after subarachnoid opioid administration.

The authors thank the South African MRC for their financial support (grant no. 1036/1) and Mr. G. Moffett and his staff in the animal colony for their technical assistance.

## References

1. Bromage PR. The price of intraspinal narcotic analgesia: basic constraints. Anesth Analg 1981;60:461–3.
2. Knill RL, Clement JL, Thompson WR. Epidural morphine causes delayed and prolonged ventilatory depression. Can Anaesth Soc J 1981;28:537–43.
3. Morgan M. Editorial. Anaesthesia 1982;33:527–9.
4. Strube PJ, Downing JW, Brock-Utne JG. CSF pharmacokinetics of extradural morphine. Br J Anaesth 1984;56:921–2.
5. Downing JW, Williams V, Hascke R, Porte D, Wood S, Fogel K, Horn J. Rostral spread of epidural morphine. Anesth Analg 1984;63:375–6.
6. Heisey SR, Held D, Pappenheimer JR. Bulk flow and diffusion in the cerebrospinal fluid system of the goat. Am J Physiol 1962;203:775–81.
7. Cserr HF. Physiology of the choroid plexus. Physiol Rev 1971;51:273–311.
8. Nielsen CH, Camporesi EM, Bromage PR, Bukowski EM, Durant PAC. $CO_2$ sensitivity after epidural and intravenous morphine. Anesthesiology 1981;55:A.372.
9. Helrich H, Papper EM, Brodie BB. The fate of intrathecal procaine and the spinal fluid level required for surgical anesthesia. J Pharmacol Exp Ther 1950;100:78–82.
10. Stanley TH. Intrathecal opiates, a potent tool to be used with caution. Anesthesiology 1980;53:523–4.

ANESTH ANALG
1985;64:933–6

## Clinical Reports

# Myocardial Ischemia due to Obstruction of an Aortocoronary Bypass Graft by Intraoperative Positioning

Chris M. Weinlander, MD, Dennis W. Coombs, MD, and Stephen K. Plume, MD

The patency of aortocoronary saphenous vein bypass grafts is greater than 80% after 5 yr (1,2). Graft obstruction requires surgery in some patients, particularly when it involves a critical coronary lesion. Causes of acute obstruction of bypass grafts that have been reported include gaseous or particulate emboli, vasospasm, and thrombosis due to low flow states (3,4). Causes of delayed onset of obstruction of grafts include intimal proliferation and fibrosis, thrombosis, and atherosclerosis (5). Mechanical causes of graft obstruction, including pressure placed directly over the sternum and graft, have not been reported. We report a case of acute reversible obstruction of flow in an 8-yr-old coronary artery bypass graft, apparently due to intraoperative positioning.

## Case Report

A 55-yr-old man was scheduled for a lumbar laminectomy for spinal stenosis. Past medical history included coronary artery bypass grafting of the left anterior descending (LAD) artery and the right coronary artery in October 1976, for angina uncontrolled by medical management. He had never had a myocardial infarction. Since that time, the patient had been free of angina. His activity had been limited over the past year, however, by low back pain. The patient also had a history of hypertension, for which he took both hydrochlorothiazide, 50 mg, twice a day and potassium supplementation. In addition to the coronary artery bypass grafts, the patient had an L4–5 discectomy in March 1977, without complications. During that operation, the patient was in the prone position and lateral chest rolls were used. Anesthesia, consisting of nitrous oxide, oxygen, thiopental, and pancuronium, was uneventful. At the time of the present admission, physical examination was unremarkable. Preoperative laboratory values were also unremarkable. The ECG showed a first degree atrioventricular (AV) block without evidence of myocardial ischemia.

After pretreatment with fentanyl, 100 μg, and gallamine, 15 mg, anesthesia was induced with 300 mg of thiopental, and tracheal intubation was carried out using 100 mg of succinylcholine. Anesthesia was maintained using nitrous oxide and oxygen, fentanyl, and pancuronium. Pulmonary ventilation was controlled, and isoflurane was used to reduce a systolic hypertension of 150 mm Hg on two occasions. The blood pressure never decreased below 100 mm Hg during the first 30 min of anesthesia.

The patient was placed in the knee–chest position on a 1080 AMSCO operating table. Considerable venous congestion of the head and neck occurred. Our solution was to place an anterior sternal roll to elevate the thorax and improve venous drainage from the head and neck. Twelve to 15 cm of sternal padding were needed to relieve the venous congestion. The operation was begun. Examination of the $V_5$ lead showed, for the first time, 1–2 mm of ST depression (single lead monitoring). The patient continued to be hemodynamically stable. A second set of electrodes and a different 7803 B Hewlett Packard electrocardiograph were used to determine whether the ECG changes were artifacts of position or equipment. Nitroglycerin, 100 μg intravenously, and propranolol, 1 mg intravenously, were given; but no change occurred in the ST segments. A nitroglycerin infusion was begun. The new ECG tracing showed a definite injury current consisting of 3–4 mm of J point and ST elevation. Thirty min after induction, the surgeons stated that they would finish the operation in another 30 min. Due to the persistent ST segment elevation, nifedipine, 10 mg, was given intranasally. It was not possible to give the nifedipine sublingually because of intraoperative positioning. Over the 5 min after intranasal nifedipine, the systolic blood pressure decreased from 150 to 90 mm Hg. No change or improvement in the ST segments occurred. Over the

---

Received from the Departments of Anesthesiology and Cardiothoracic Surgery, Dartmouth–Hitchcock Medical Center, Hanover, New Hampshire. Accepted for publication April 29, 1985.

Address correpondence to Dr. Weinlander, Department of Anesthesiology, Dartmouth–Hitchcock Medical Center, Hanover, NH 03756.

© 1985 by the International Anesthesia Research Society

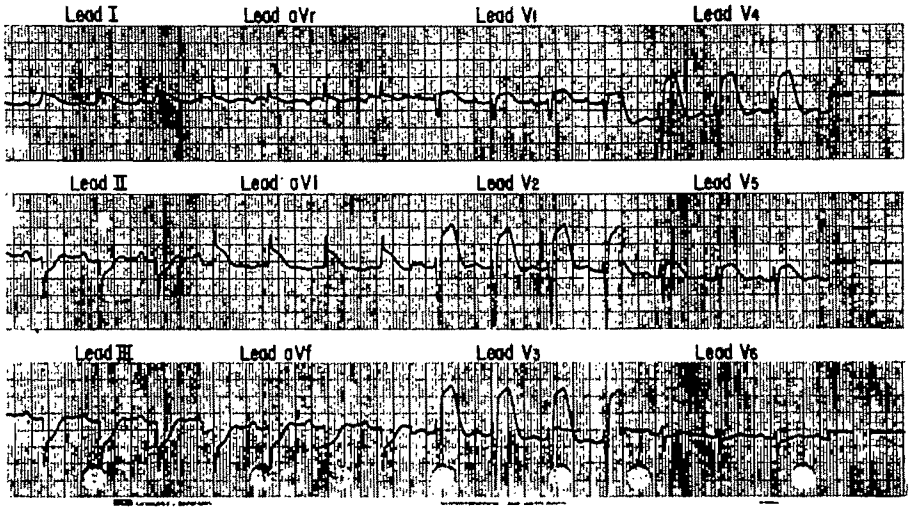


Figure 1. Initial ECG done in the recovery room after completion of lumbar laminectomy and before acute revascularization of the LAD artery; one hour after placement of sternal padding. The patient was receiving 100% $F_{I_{O_2}}$. Acute anterolateral ischemic changes are present. Calibration voltage of the ECG is 10 mm.

next 10 min, the systolic pressure gradually increased to 120 mm Hg. Fifty min after induction of anesthesia, the patient had a 6-beat run of ventricular tachycardia. A bolus injection of 75 mg of lidocaine was given followed by infusion of lidocaine at a rate of 3 mg/min. A radial arterial catheter was inserted, and the nitrous oxide was discontinued. An arterial blood sample showed the pH to be 7.32, $P_{CO_2}$ to be 44 mm Hg, and $P_{O_2}$ to be 487 mm Hg.

At the completion of surgery, the patient's systolic blood pressure decreased to 60 mm Hg. This initially responded to injection of ephedrine, 12.5 mg intravenously, and calcium chloride, 500 mg intravenously. A dopamine infusion at a rate of 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was started, and 300 ml of lactated Ringer's solution was administered. The rate of infusion of dopamine was increased and reached 15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ on arrival in the recovery room to maintain a blood pressure of 70–80 mm Hg. A 12-lead ECG showed evidence of massive anterolateral ischemia consistent with a lesion in the distribution of the LAD artery (Fig. 1). A pulmonary artery catheter was inserted. The initial pulmonary artery pressure was 23/16 mm Hg with a pulmonary capillary wedge pressure of 14 mm Hg. The cardiac output was 3.5 L/min.

After consultation with cardiologists and cardiothoracic surgeons, it was agreed that the patient was suffering an acute anterolateral myocardial infarction. Blood sampled at that time later revealed a creatine phosphokinase level of 3040 IU/L (upper limit of normal 225 IU/L) with a 10% MB fraction (normal MB fraction 4%). An intraaortic balloon pump (IABP) was inserted preparatory to emergency coronary revascularization. Cardiac catheterization was not performed, in order to avoid delaying revascularization. The patient was anesthetized with 5 mg fentanyl, 10 mg pancuronium, and 100% oxygen. The right common femoral artery and vein were exposed. Heparin was administered and the groin vessels cannulated. Cardiopulmonary bypass was begun, and the patient's core temperature was decreased to 32°C. The sternum was then bisected and adhesions taken down sufficiently to define the anterior surface of the heart. A second venous cannula was inserted via the right atrial appendage, and a transatrial left ventricular vent was inserted via the right superior pulmonary vein. The LAD artery was dissected free. Both saphenous vein bypass grafts were patent and pulsatile. Flow was audible by Doppler examination through both vessels. An end-to-side anastomosis was made between the LAD artery distal to the previously inserted graft and the aortic root. Termination of cardiopulmonary bypass required epinephrine, nitroglycerin, and sodium nitroprusside infusions to maintain a cardiac output of 4.5 L/min. The IABP was continued intraoperatively and for 48 hr postoperatively.

The patient recovered from the operation without incident and left the hospital on the eighth postoperative day. An ECG done on the sixth postoperative day is shown in Figure 2. A thallium exercise tolerance test to 6 METs (one MET unit is equal to the basal oxygen consumption, about 3.3–3.5 $ml \cdot kg^{-1} \cdot min^{-1}$) was performed 6 weeks postoperatively and was consistent with an old anteroseptal myocardial infarction. The patient had no chest pain or evidence of ischemia during this stress test. The patient had no complaints of low back pain or chest pain after discharge. He refused a followup cardiac catheterization.

## Discussion

In this patient, the temporal sequence of events strongly suggests that the act of placing the sternal padding

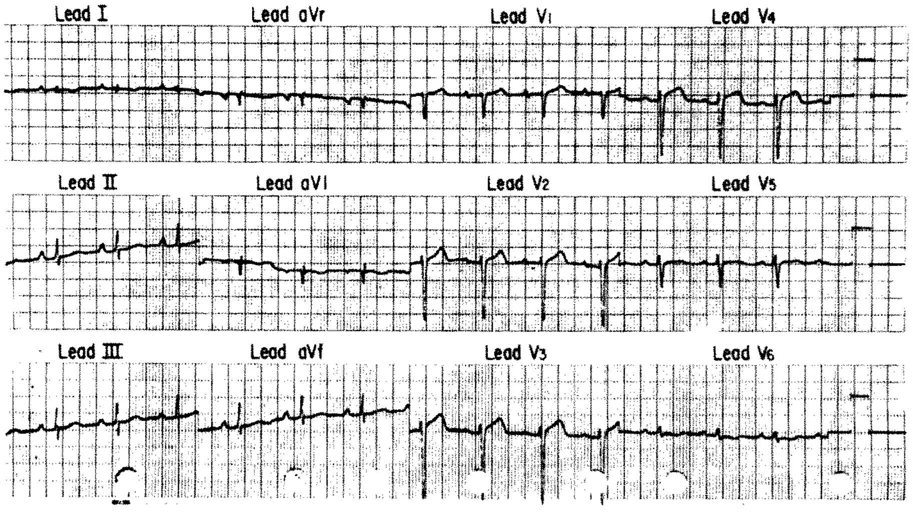


Figure 2. ECG on the sixth postoperative day showing resolution of the injury current and persistent nondiagnostic lateral T-wave changes. The patient was an ambulatory inpatient without supplemental oxygen therapy. Calibration voltage of the ECG is 10 mm.

directly over the graft on the LAD artery precipitated acute obstruction of flow in the graft. This caused myocardial ischemia in the area of distribution of the LAD coronary artery as evidenced by changes in the ECG and cardiac enzyme levels before exploration of the grafts (Fig. 1). This possibility also is supported by the fact that the patient had had a previous procedure on the lower back after his initial coronary artery bypass graft without incident. The major difference between this operation and the first operation on his back was one of positioning. We are aware of no data demonstrating adverse effects of prone or knee–chest position on myocardial function. Smith states that he has "never seen impairment of cardiac efficiency develop because the weight of the body was supported on the chest wall" (6). Thus in the absence of other factors such as hypoxia or hypotension, onset of ischemia is otherwise unexplained. Indeed, the ischemic changes occurred after placement of the sternal padding, and no significant hypotensive event occurred before or for 30 min after its placement.

Mechanical events can trigger myocardial ischemia involving coronary vein bypass grafts. For example, the length of the vein graft is critical. If it is too short, it may kink at the anastomotic site or be intermittently compressed by the heart during diastolic filling. If long, the graft is similarly susceptible to kinking. As time passes, the graft becomes partially encased in fibrosis and adhesions, to some extent protecting it from kinking and compression. Unlike the intramyocardial artery, however, no myocardial bridging supports this structure during diastole (7). Processes such as atherosclerosis and intimal proliferation may have further predisposed this patient's graft to obstruction by mechanical factors. Obstruction of flow may have been due to direct compression of the lumen of the graft. More likely, however, gravity, compression, and associated mechanical factors led to kinking of this rigid and partially occluded graft. This, in turn, led to a narrowing of the lumen and resultant obstruction of flow.

Other causes of myocardial ischemia in this patient cannot be unequivocally ruled out. For instance, it is possible that coronary artery spasm may have occurred. In a recent clinical report by Skarvan et al., coronary artery spasm occurring between the termination of cardiopulmonary bypass and 150 min after completion of the operation was treated with either intravenous (0.8–2 mg) or sublingual (20 mg) nifedipine or intracoronary nitroglycerin (8). Hemodynamic function stabilized within 15–120 min after the start of the treatment, indicating that spasm had been treated successfully. If vasospasm did occur in our patient, it did not respond to treatment with nifedipine. This lack of a salutary effect on an evolving myocardial infarction was also noted by Muller et al. in the Nifedipine Angina Myocardial Infarction Study (9). In that study, nifedipine (20 mg orally every 6 hr starting 4.6 hr after the onset of chest pain) failed to prevent progression of a threatened infarction to an acute myocardial infarction or to reduce infarct size. Although the nifedipine was administered intranasally in our case, it produced a systemic response, as evidenced by the decrease in systolic blood pressure from 150 to 90 mm Hg. The pulsatile and patent state of the grafts at the time of exploration also argues against the possibility of vasospasm.

Most patients with acute perioperative myocardial infarctions do not undergo immediate coronary revascularization. There is a rationale, however, for this aggressive approach. Our decision to proceed with acute revascularization was made in the presence of acute hemodynamic instability and evolving myocardial infarction, and in attempt to preserve as much viable myocardium as possible. In an animal study, Costantini et al. compared two groups of dogs (10). One group had 7 days of continuous occlusion of the proximal LAD artery. A second group had 3 hr of occlusion followed by 7 days of reperfusion of the same artery. In the first group, mechanical and metabolic function remained severely depressed after 7 days of occlusion. Mean infarct size was 31.6%. In the second group, significant mechanical and metabolic dysfunction developed and did not improve during the first hour of reperfusion. After 7 days of reperfusion, however, function had returned to near preocclusion levels. Mean infarct size was 14.2%. A study by Phillips et al. examined surgery for evolving myocardial infarction in humans (11). One hundred and fifty-six patients underwent emergency coronary revascularization during evolving myocardial infarctions as demonstrated by ECG, cardiac enzyme levels, and clinical course. Catheterization revealed double- or triple-vessel disease with the arteries not responsible for the myocardial infarction having lesions of 70% or greater. Single-vessel disease was excluded unless a single artery supplied approximately 15% or more of the myocardial mass (proportion of nonmoving wall to moving wall). The average time from the onset of chest pain to complete revascularization was 6 hr. Thrombectomy was successfully performed in 79% of patients. The surgical mortality was 5.1%. Average improvement in ejection fraction among a subgroup of patients ($n$ = 26) who, like our patient, were hypotensive, receiving drug therapy, or on IABP support preoperatively was 56% (from 29% to 44%). Graft patency was 99% on restudy. Late followup to 62 months disclosed only 17 patients with residual limitations. Both of these studies support the decision to proceed with emergency coronary revascularization in the setting of an evolving myocardial infarction. Due to the hemodynamic instability of our patient, it was felt that exploration and revascularization should be performed as soon as possible without waiting for cardiac catheterization.

In conclusion, the sequence of events in this case strongly suggests that a position-related occlusion of a previously patent aortocoronary bypass graft led to myocardial infarction. The patient went on to have acute coronary revascularization with a good outcome. Although a rare event, mechanical occlusion of coronary bypass grafts may occur. If suspected, strong consideration should be given to measures directed toward reversing the occlusion, including acute thrombectomy, revascularization, or both.

The authors thank Kristin Lanphear for manuscript preparation and Drs. Quentin J. Durward and Bruce D. Hettleman, of the Sections of Neurosurgery and Cardiology, respectively, for their involvement in this case.

## References

1. Uricchio JF, Bentivoglio LG. Patency of saphenous vein grafts five or more years after coronary bypass surgery. Am J Med 1978;65:619–26.
2. Lawrie GM, Lie JT, Morris GC, Beazley HL. Vein graft patency and intimal proliferation after aortocoronary bypass: early and long-term angiopathologic correlations. Am J Cardiol 1976;38:856–62.
3. Keon WJ, Heggtveit HA, Leduc J. Perioperative myocardial infarction caused by atheroembolism. J Thorac Cardiovasc Surg 1982;84:849–55.
4. Victor MF, Kimbiris D, Iskandrian AS, et al. Spasm of a saphenous vein bypass graft–a possible mechanism for occlusion of the venous graft. Chest 1981;80:814–5.
5. Kern WH, Wells WJ, Meyer BW. The pathology of surgically excised aortocoronary saphenous vein bypas grafts. Am J Surg Path 1981;5:491–6.
6. Smith RH. The prone position. In: Martin JT. Positioning in anesthesia and surgery. Philadelphia: WB Saunders, 1978:32–43.
7. Angelini P, Trevillato M, Donis J, Leachman RD. Myocardial bridges: a review. Prog in Cardiovasc Dis 1983;26:75–88.
8. Skarvan K, Graedel E, Hasse J, Stulz P, Pfisterer M. Coronary artery spasms after coronary artery bypass surgery. Anesthesiology 1984;61:323–7.
9. Muller JE, Morrison J, Stone PH, et al. Nifedipine therapy for patients with threatened and acute myocardial infarction: a randomized, double-blind, placebo-controlled comparison. Circulation 1984;69:740–7.
10. Constantini C, Corday E, Lang T, et al. Revascularization after 3 hours of coronary arterial occlusion: effects on regional cardiac metabolic function and infarct size. Am J Cardiol 1975;36:368–84.
11. Phillips SJ, Zeff RH, Kongtahworn C, et al. Surgery for evolving myocardial infarction. JAMA 1982;248:1325–8.

ANESTH ANALG
1985;64:937–40

# Paraplegia Caused by Spinal Angioma—Possible Association with Epidural Analgesia

Nicholas P. Hirsch, FFARCS, Christopher S. Child, FFARCS, and S. A. Wijetilleka, FFARCSI

Epidural analgesia is a widely accepted technique for providing pain relief during labor. However, both transient and permanent neurologic sequelae, including paraplegia, have been reported (1–6). We report a case in which the administration of epidural analgesia was followed over the next few weeks by a progressive paraplegia. Investigations demonstrated the presence of a spinal arteriovenous malformation (AVM). A mechanism is proposed by which the epidural injection may have caused a change in blood flow through the AVM resulting in cord ischemia.

## Case History

The patient was a fit 41-year-old woman whose only previous medical history was that of hypertension associated with the use of an oral contraceptive. Her three previous pregnancies had all culminated in normal deliveries, the last twenty years earlier. She had not received epidural analgesia during her previous confinements, and there had been no obstetric complications. During the sixteenth week of her fourth pregnancy she was found to be hypertensive (145/104 mm Hg), and she was treated with methyldopa, 250 mg, three times per day, later reduced to 250 mg twice a day, which produced satisfactory control of her blood pressure.

After unsuccessful attempts to induce labor with dinoprostone (prostin $E_2$) pessaries when the patient reached term, it was decided to induce labor with an oxytocin infusion and to provide control of pain and blood pressure with epidural analgesia. After an infusion of 500 ml of Ringer's lactate solution, an epidural catheter was introduced without difficulty into the L4/L5 interspace via a Tuohy needle with the patient in the left lateral position. A test dose of 2 ml of 0.5% bupivacaine resulted in no untoward effects, and the full dose of 8 ml of 0.5% bupivacaine was administered after oxytocin-induced labor was fully established; no hypotension occurred. Ten minutes after the administration of the local analgesic, the patient complained of a dull pain in her neck and left arm that subsided spontaneously after several hours. The pain was not related to contractions, straining, or posture. The second stage of labor lasted for one hour, and she delivered a healthy boy by spontaneous vaginal delivery. When discharged from the hospital seven days after delivery, she did not complain of any symptoms. However, the pain in her arm and neck recurred intermittently, and four weeks after discharge she developed weakness and numbness of both legs that progressively worsened. Five weeks after discharge she was readmitted to hospital unable to walk and with urinary retention. During the 24 hr after admission, she developed weakness of both arms, more severe on the left. On examination the signs were suggestive of an upper motor neuron lesion. At this stage her respiration was noted to be entirely diaphragmatic, and she was closely observed for signs of phrenic paralysis. Studies at this time included a lumbar puncture, which showed the CSF to be clear, and an Iohexol myelogram, which revealed dilated and tortuous vessels throughout the length of the spinal canal (Fig. 1). These were more prominent in the cervical region and were accompanied by mild swelling of the cervical cord. It was concluded that these findings were suggestive of a cervical cord angioma, and angiography performed four weeks later confirmed the presence of a large dural arteriovenous malformation arising from the left vertebral artery at the level of the foramen magnum (Fig. 2). The vessel feeding the malformation was successfully clipped at operation; although the patient's clinical signs remained essentially the same, there was some improvement in motor function in both hands after the operation.

---

Received from the Department of Anaesthesia, The National Hospital for Nervous Diseases, Queen Square, London and the Department of Anaesthesia, The Ipswich Hospital, Ipswich, Suffolk, United Kingdom. Accepted for publication April 4, 1985.

Address correspondence to Dr. Hirsch, Department of Anesthesia, Yale-New Haven Hospital, New Haven, CT 06510.

© 1985 by the International Anesthesia Research Society

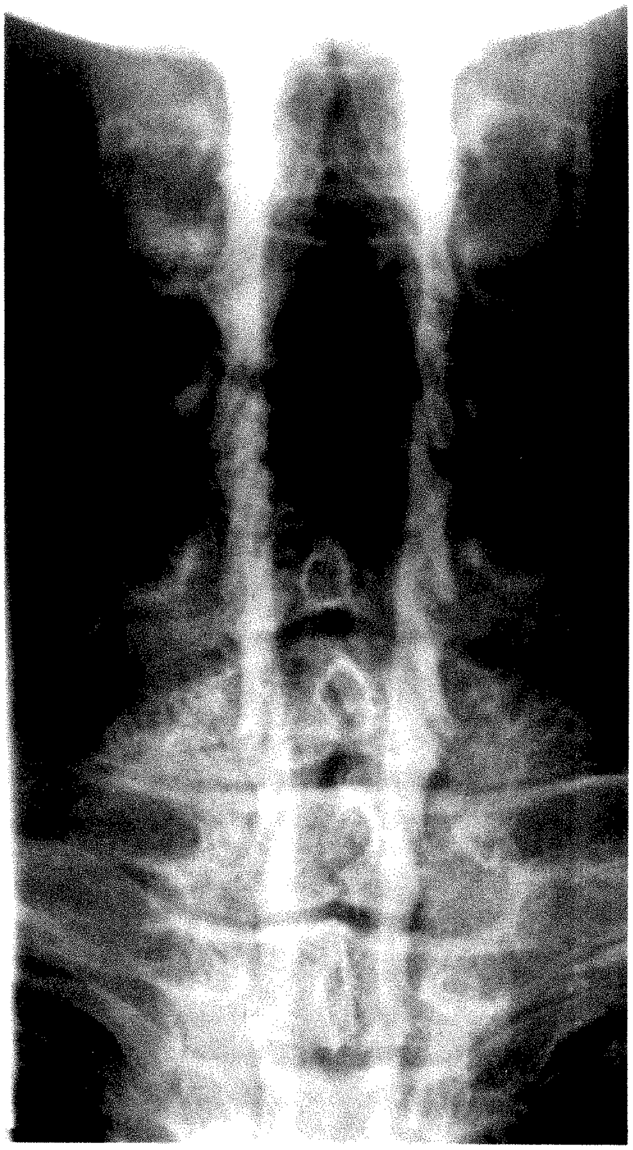


Figure 1. Iohexol myelogram revealing dilated, tortuous vessels.

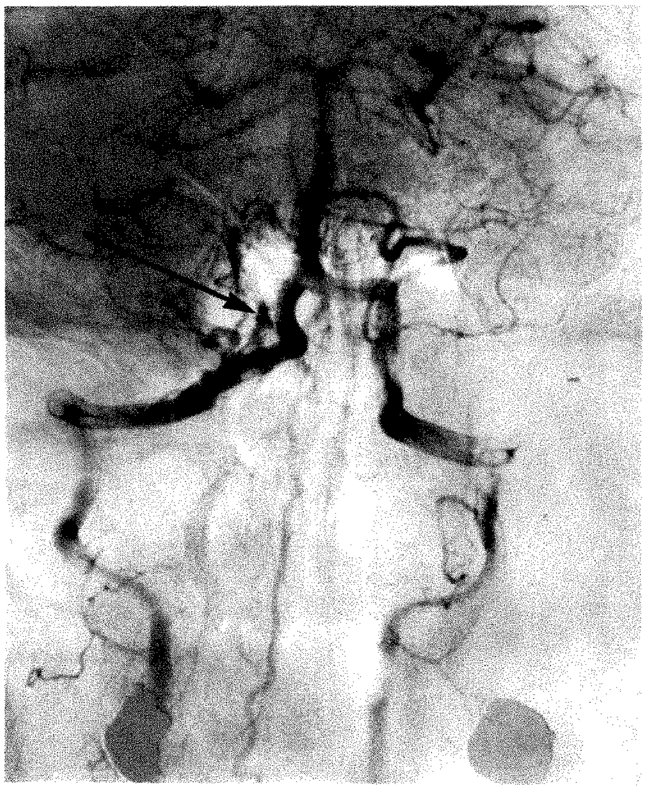


Figure 2. Arteriovenous malformation (arrow) arising from the left vertebral artery at the level of the foramen magnum.

## Discussion

Spinal angiomas are uncommon, their incidence being between 3.4 and 11.5% of spinal cord tumors (7,8). However, these AVMs have been recognized with increasing frequency since the introduction of improved contrast myelography and selective spinal angiography. Most spinal angiomas are found in the thoraco–lumbar region and are said to be 2–3 times more common in males. When located in the cervico–thoracic region, incidence is approximately equal in both sexes. In about 60% of cases the diagnosis is reached before the age of forty (9). Patients typically present with pain in the back, neck, or limbs, with other sensory signs, or with weakness. Other less common presenting features are a disturbance of micturition, of defecation, or of sexual function. Symptoms characteristically commence insidiously unless spinal subarachnoid hemorrhage occurs; however, the latter is the presenting feature in only 5% of cases (10).

Symptoms of spinal angiomas may be precipitated or aggravated by exercise, systemic infection, unrelated trauma, and menstruation (11). Pregnancy has been reported as occasionally provoking symptoms, and suggested mechanisms include an increased venous pressure due to inferior vena cava compression by the gravid uterus (12), hormonal changes affecting the vascular endothelium (13), and an increase in blood volume (14).

The mechanism that leads to the development of neurologic deficit in patients with spinal angiomas is uncertain, but it appears that an alteration in the venous pressure in the vessels draining these vascular tumors is an important factor (15,16). The venous drainage of the cord is shown in Figure 3. It can be

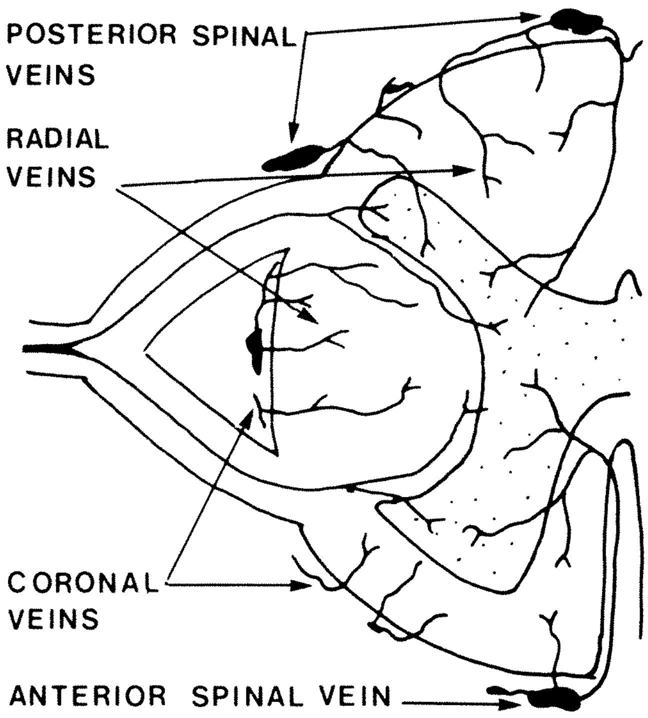


Figure 3. Venous drainage of the spinal cord.

seen that the coronal veins receive blood from the radial veins that drain the intramedullary circulation. The coronal veins in turn empty into the epidural venous plexus. Symon et al. (17) have suggested that when a spinal angioma is present there is an increase in pressure in both the coronal and epidural veins. This results in a decreased arteriovenous (A–V) pressure gradient and a decreased spinal blood flow. The reduced A–V pressure gradient in turn leads to intramedullary vasodilatation and to the development of increased tissue pressure. These intravascular pressure changes are transmitted directly to the adjacent cord substance, resulting in the formation of edema. Ultimately, if unchecked, extensive ischemic damage of the cord may result.

In this case there are a number of factors that could have altered the already compromised venous drainage of the angioma, thereby precipitating spinal cord damage by the mechanism outlined above. Uterine contraction results in increased venous pressures within the epidural plexus, and this is reflected in the increases in epidural pressure that have been observed during labor (18). Similarly, the Valsalva-like maneuver of bearing down forces blood into the entire epidural plexus, and this results in very high pressure peaks throughout the whole of the epidural space (19). Presumably, postpartum uterine contraction also increases pressures within the epidural venous system. These factors, whether alone or in combination, could have contributed to an alteration of the hemodynamics of the angioma.

The apparent temporal relationship between the epidural injection and the onset of pain in the arm and neck is difficult to explain. However, it is documented that the introduction of liquid into the epidural space leads to an increase of pressure in the space (20). This pressure change is transmitted to the epidural veins, and this could have compromised further the venous drainage of the angioma. However, despite the reduced compliance of the epidural space in pregnancy, the increase in epidural pressure after epidural injection is not sustained, and it is difficult to imagine such a short-lived increase in pressure resulting in such devastating neurological deficit so long after the injection.

In conclusion, a case is described in which the onset of symptoms due to a cervical angioma was associated with, but not necessarily caused by, an epidural injection. Symptoms included pain in the neck and arm followed by progressive paraplegia. The pathophysiology of spinal angiomas is discussed, and possible mechanisms are proposed to explain the development of the neurological deficit.

## References

1. Usubiaga JE. Neurological complications following epidural anaesthesia. International Anesthesiology Clinics 1975;13:3,29.
2. Chaudhair LS, Kop BR, Ohruva AJ. Paraplegia and epidural analgesia. Anaesthesia 1978;33:772–5.
3. Newman B. Post-natal paraparesis following epidural analgesia and forceps delivery. Anaesthesia 1983;38:350–1.
4. Balin NC. Paraplegia following epidural analgesia. Anaesthesia 1981;36:952–3.
5. Hirlekar G. Paraplegia after epidural analgesia associated with an extradural spinal tumour. Anaesthesia 1980;35:363–4.
6. Kane RE. Neurological deficits following epidural or spinal anesthesia. Anesth Analg 1981;60:150–61.
7. Krayenbuhl H, Yasergil MG. Die varicosis Spinalis und ihre Behandlung. Schweiz Arch Neurol Neurochir Psychiatr 1963;92:74–92.
8. Pia HW, Vogelsang H. Diagnose und Therapie spinaler Angiome. Deutsch Z Nervenheilk 1965;187:74–96.
9. Aminoff MJ. Spinal angiomas, 1st ed. Oxford:Blackwell Scientific Publications, 1976:34.
10. Aminoff MJ, Logue V. Clinical features of spinal vascular malformations. Brain 1974;97:211–8.
11. Pia HW. Diagnosis and treatment of spinal angiomas. Acta Neurochir 1973;28:1–12.
12. Nelson DA. Spinal cord compression due to vertebral angiomas during pregnancy. Arch Neurol 1964;11:408–13.
13. Epstein FA, Beller AJ, Cohen I. Arterial anomalies of spinal cord. J Neurosurg 1949;6:45–56.
14. Newquist RE, Mayfield FH. Spinal angioma presenting during pregnancy. J Neurosurg 1960;17:541–5.

15. Aminoff MJ, Barnard RO, Logue V. The pathophysiology of spinal vascular malformations. J Neurol Sci 1974;23:255–63.
16. Kendall BE, Logue V. Spinal epidural angiomatous malformations draining into intrathecal veins. Neuroradiology 1977;13:181–9.
17. Symon L, Hideyuki K, Kendall BE. Dural arteriovenous malformations of the spine. J Neurosurg 1984;60:238–47.
18. Galbert MW, Marx GF. Extradural pressures in the parturient patient. Anesthesiology 1974;40:499.
19. Usubiaga JE, Moya F, Usubiaga LE. Effect of thoracic and abdominal pressure changes on the epidural space pressure. Br J Anaesth 1967;39:612.
20. Husemeyer RP, White DC. Lumbar extradural injection pressures in pregnant women. Br J Anaesth 1980;52:55–60.

# Letters to the Editor

## Balanced Anesthesia: Does it Anesthetize?

To the Editor:

I am prompted by the letter from Dr. Grummitt (Anesth Analg 1984;63:1049) in which he takes issue with a statement that "the level of surgical stimulation" may be too intense and continuous to achieve adequate anesthesia with a nitrous oxide–narcotic relaxant technique. I have recently completed a study comparing the incidence of awareness and wakefulness between a balanced anesthetic technique and a total intravenous anesthetic technique. Wakefulness is the ability of a patient to respond to a command during general anesthesia but then to have no recollection of this in the postoperative period (1). I say completed, but in fact I terminated the investigation at the halfway point because so many patients were wakeful that moral and ethical doubts were raised about its continuation.

The technique of balanced anesthesia consisted of premedication with oral temazepam (10–20 mg) one hr preoperatively. Anesthesia was induced with fentanyl 250 $\mu$g, thiopental (3–4 mg·kg$^{-1}$), and succinylcholine (1–1.5 mg·kg$^{-1}$). After intubation the patients' lungs were artificially ventilated with 66% nitrous oxide in oxygen from a nonrebreathing circuit. The minute volume was 100 ml·kg$^{-1}$·min$^{-1}$ and the tidal volume was set at 10 ml·kg$^{-1}$. Muscle relaxation, as dictated by surgical requirements, was maintained with incremental injection of vecuronium. Further fentanyl (100 $\mu$g) was injected as indicated by clinical signs of light anesthesia, and thiopental (100 mg) plus fentanyl (100 $\mu$g) were given when wakefulness was detected. Wakefulness was assessed by using a modification (2) of Tunstall's (1,3) isolated arm technique.

The results for the balanced anesthetic shown in Table 1 are by no means unique. Wilson (4) found that approximately 30% of patients could respond to commands during surgery when papaveretum had been used for premedication and also as part of the balanced technique. Tunstall (3) has shown this wakeful anesthetic state occurring in more than 75% of mothers at some stage during cesarean section under general anesthesia.

Despite the high incidence of wakefulness in this study, only one patient had factual recall. However, it should be remembered that after wakefulness had been double-checked by holding the patient's hand and giving her further specific instructions, thiopental (100 mg) was injected intravenously. Without this the incidence of awareness may have been much higher.

Table 1. The Outcome of Balanced Anesthesia

| | Nitrous oxide–oxygen and fentanyl |
|---|---|
| Number of patients | 25 |
| Technique abandoned because of high blood pressure | 2 |
| Number of patients showing purposeful movements of isolated arm | 18 |
| Number of patients moving hand in response to commands | 11 |
| Number of patients opening their eyes during surgery | 9 |
| Number of patients given supplementary thiopental | 12 |
| Nightmares | 4 |
| Other dreams | 1 |
| Recall | 1 |
| Mean duration of anesthesia and range (min) | 70 (40–130) |
| Mean dose of fentanyl and range ($\mu$g) | 450 (250–750) |
| Mean dose of fentanyl per hr ($\mu$g) | 400 |
| Mean weight of patients and range ($\mu$g) | 62 (43–80) |

Four patients had nightmares, either during or after surgery, and these were typical of light anesthesia. Two patients were initially reluctant to discuss these nightmares in case they were interpreted as signs of impending insanity. One patient thought she was a bee crawling on a page while someone tried to cut her in half; another page would then fall on top of her and all was peace for a time until she crawled out again to repeat the process. The second patient dreamt she was being buried while she cried out, "I'm not dead yet," but no one could hear her. The third patient dreamt she was blind and was unable to open her eyes. The fourth patient experienced the same nightmare as she had experienced with three previous "balanced" techniques using various combinations of fentanyl and droperidol. She floated dispassionately up in the air viewing herself below, all alone on earth, frightened, and with no one to talk to. I have since anesthetized her again for yet further major surgery (this time using papavertum and halothane 0.5–1%) after which, to her immense relief, there were no dreams. All four of these patients responded to

© 1985 by the International Anesthesia Research Society

commands at some stage during surgery, but only the fourth had actual recall of what was said to her during surgery. Despite my doubts about this technique, all patients who had previous experience of general anesthesia felt that in terms of postoperative well being this was their anesthetic of choice for the future.

I cannot comment about the risks of wakefulness in balanced anesthesia in general because many techniques and drugs are used, e.g., older analgesics with a hypnotic component like morphine, or the addition of droperidol. However, the technique as described, usually with much less fentanyl and much more muscle relaxant, is sufficiently widespread that I feel obliged to communicate these results.

With the limited data available, it is up to the reader to decide, if the results, in Dr. Grummitt's words (5), "strike at the very foundation upon which the technique of balanced anesthesia has been built."

Ian F. Russell, FFARCS
*Department of Anesthesia*
*Hull Royal Infirmary*
*Anlaby Road*
*Hull, HU3 2JZ, England*

## References

1. Tunstall ME. Detecting wakefulness during general anaesthesia for caesarean section. Br Med J 1977;1:1321.
2. Russell IF. Auditory perception under anaesthesia. Anaesthesia 1979;34:211.
3. Tunstall ME. The reduction of amnesic wakefulness during caesarean section. Anaesthesia 1979;34:316–9.
4. Wilson ME. Awareness in general anaesthesia. Br Med J 1980;280:1270.
5. Grummitt RM. Balanced anesthesia does anesthetize. Anesth Analg 1984;63:1049.

---

# A Bellow's Leak in an Ohio Anesthesia Ventilator

To the Editor:

A recent case illustrates the need for proper preoperative testing of ventilator bellows used during anesthesia. Shortly after an Ohio 7000 ventilator began to control respiration in a patient undergoing knee arthroscopic examination under general anesthesia, it was noted that the bellows was not rising at the end of exhalation. The patient's chest was rising with each inhalation, a peak inspiratory pressure of 26 cm $H_2O$ was attained, the vital signs remained stable, and a respirometer showed the exhaled tidal volume to be 850 ml. The ventilator was adequately ventilating the patient at the volume set without detrimental effects. Inspection of the ventilator revealed a loose connection between the bellows and bellows base assembly. After correction of the problem, the ventilator produced similar respirometer readings. The operation and postoperative course were uneventful.

The Ohio 7000 anesthesia ventilator uses two separate gas circuits: the pneumatic driving gas and the patient–bellows breathing circuit. A leak in the bellows converts the two separate gas systems into a single system. although the patient suffered no ill effects, the potential consequences might be dilution of anesthetic gas and a light or awake patient, pulmonary barotrauma (a maximum inspiratory pressure of 65 cm $H_2O$ can be achieved with the Ohio 7000 ventilator), and impedance to exhalation (PEEP) if pressure in the housing surrounding the bellows increases above atmospheric pressure. Preoperative testing of the ventilator system required obtaining additional diagrams and information from the Ohio company. There is no specific bellows leak test, although two functional ventilator preoperative tests cannot be performed if there is a significant leak in the bellows. The bellows material test checks the bellows compliance and involves inflation of the bellows to 100 ml in a closed system. The test should result in a pressure less than 1.75 cm $H_2O$ when the needle valve is closed. The pop-off valve test requires an $O_2$ flow of 300 ml/min in a closed circle. The bellows should rise to the top of the bellows housing, and the pressure gauge should indicate less than 2.5 cm $H_2O$.

This case illustrates improper, though adequate, function of the Ohio 7000 ventilator despite a leak in the bellows. Bellows leaks can create an unsafe situation; the manufacturer's manuals are inadequate. Some of the potential complications can occur with one breath, and therefore, preoperative testing of the bellows tightness is recommended.

Charles H. Ripp, MD
James W. Chapin, MD
*Department of Anesthesiology*
*University of Nebraska Medical Center*
*42nd & Dewey Avenue*
*Omaha, NE 68105*

---

# Ordering Priorities: Improved Anesthesia or Surgery—the Case of Cordotomy

To the Editor:

Dautenhahn et al. (1) present an interesting and viable anesthetic technique for open cordotomy. However, it should be recognized by anesthesiologists that this is an obsolete surgical procedure that has been replaced by cervical percutaneous radiofrequency spinothalamic tractotomy (2,3). The latter is more predictable, safer, and needs only neuroleptanalgesia.

Perry G. Fine, MD
*Irene Eleanor Smythe Pain Clinic*
*Department of Anesthesia, University of Toronto*
*Bell Wing 3-640*
*Toronto General Hospital*
*Toronto, Ontario, M5G IL7*
*Canada*

## References

1. Dautenhahn D, Reynolds AF, Darby R, Fagraeus L. Thoracic epidural analgesia for open cordotomy. Anesth Analg 1984;63:1036–8.
2. Tasker RR. Percutaneous cordotomy—the lateral high cervical technique. In: Schmidek HH, Sweet WH, eds. Operative neurosurgical techniques—indications, methods and results, vol 2. New York: Grune and Stratton, 1982:1137–53.
3. Lipton S. Percutaneous cordotomy. In: Wall PD, Melzack R, eds. Textbook of pain. New York: Churchill Livingstone, 1984:632–8.

# Myoclonus on Recovery from Etomidate

To the Editor:

I read with interest the report of Drs. Laughlin and Newberg (Anesth Analg 1985;64:80–2) of prolonged myoclonus after etomidate anesthesia. I often have used etomidate to induce brief general anesthesia for electrical cardioversion, hoping to take advantage of its reported hemodynamic benignity. While content with its cardiovascular effects, I have been struck by the nearly uniform occurrence of marked myoclonus on recovery lasting approximately 3–5 min. Although causing no apparent hazard, this myoclonus occasionally has perturbed cardiologists. It also renders electrocardiographic interpretation quite difficult for a brief but important period. The newly budding concern over etomidate's impairment of adrenocortical competence may also weigh in one's decision to use this drug, even for brief procedures, in the same very ill patients who could most benefit from the hemodynamic stability it may offer.

Mark D. Tasch, MD
*Department of Anesthesia*
*Indiana University School of Medicine*
*Indianapolis, IN 46223*

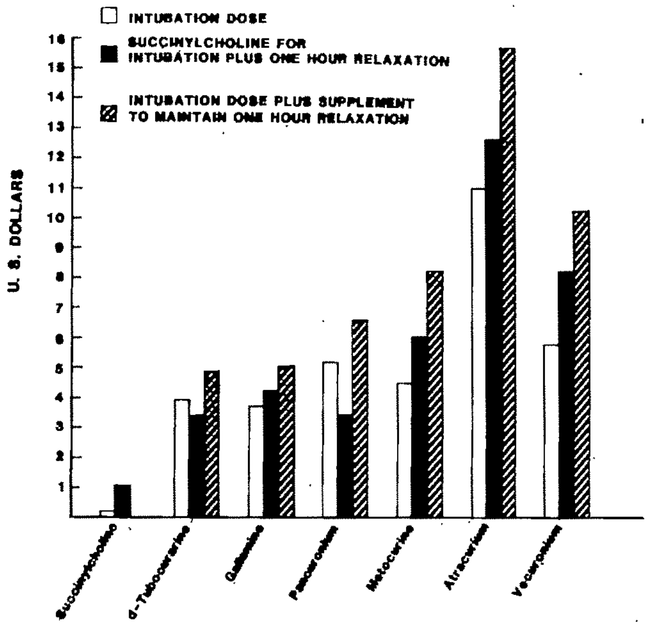


Figure 1. The cost in US dollars are shown for the various muscle relaxant drugs when administered for tracheal intubation only (white column), for relaxation for 1 hr period after intubation with succinylcholine (black column), and tracheal intubation and relaxation for 1 hr with the same drug (shaded column).

# Cost of Muscle Relaxant Drugs

To the Editor:

With the current concern for the rising costs of health care, we may have to analyze more closely the cost of the drugs that we employ in our daily practice. For example, how cost effective are the two new relaxants introduced in the last year when compared to other relaxants? To answer this we calculated the cost of muscle relaxants more commonly administered when used under three different situations for different purposes: the dose required for tracheal intubation, the amount needed to obtain adequate relaxation for one hr after intubation with succinylcholine, and the amount needed for intubation and relaxation for one hr with the same drug. The costs are shown in Figure 1. Costs for each drug in the form available, as well as the estimated dosages for the different purposes are depicted in Table 1.

Without questioning the important advantages the new muscle relaxants have brought about in cases when cardiovascular stability is highly desirable (1), and when the usual organ systems for metabolic pathways are impeded (2), use

Table 1. Comparative Doses for Various Muscle Relaxant Drugs

| Muscle relaxant drug | Intubation dose 70 kg pt (mg) | Duration of relaxation (min) | Approximate total doses for 1 hour procedure | |
|---|---|---|---|---|
| | | | With succx (mg) | Without succx (mg) |
| Succinylcholine (200 mg = $0.45) | 100 | 3–5 | 250–350 | NA |
| *d*-Tubocurarine (30 mg = $3.25) | 36 | 35 | 27 | 45 |
| Gallamine (200 mg = $4.29) | 180 | 27 | 180 | 240 |
| Pancuronium (5 mg = $4.32) | 6 | 40–45 | 4 | 8 |
| Metocurine (40 mg = $10.02) | 18 | 35 | 24 | 32 |
| Atracurium (50 mg = $15.67) | 35 | 30 | 40 | 50 |
| Vecuronium (10 mg = $10.20) | 5.6 | 28 | 8 | 10 |

Succx, succinylcholine.
( ) usual presentation forms value in U.S. dollars.

of these two new drugs in the healthy patient adds unnecessarily to the cost of anesthetic care as a whole, without obvious justifiable improvement.

J. Antonio Aldrete, MD, MS
Peter L. Hendricks, MD
*Department of Anesthesiology*
*The University of Alabama at Birmingham*
*Birmingham, AL 35233*

References

1. Robertson EN, Booij LHD, Fragen RJ, et al. Clinical comparison of atracurium and vecuronium. Br J Anaesth 1983;55:125–9.
2. Conner CS. Atracurium and vecuronium; two unique neuromuscular blocking agents. Drug Intell Clin Pharm 1984;18:714–6.

---

# Anaphylactoid Reaction to Pancuronium

To the Editor:

We were most interested in the case of anaphylactoid reaction to pancuronium reported by S. Mishima and T. Yamamura (Anesth Analg 1984;63:865–6). However, we do not agree with their conclusion that a nonspecific histamine release was involved rather than anaphylaxis. First, pancuronium is a poor histamine releaser, much worse than *d*-tubocurarine and succinylcholine, both of which were well tolerated by the patient. The skin test with succinylcholine was also negative. Our current practice of skin testing with muscle relaxants leads us to assume that pancuronium, when diluted 1/1000, never gives a positive skin test that could be related to nonspecific histamine release. Besides histamine release leads to an immediate wheal and flare reaction that disappears in less than 30 min. The delayed reaction that is quoted in this case might be due to inflammatory chemical mediators of anaphylaxis, such as IF-A, $LTB_4$, and NCF-A.

On the other hand, crossed anaphylaxis between muscle relaxants is a frequent phenomenon (1–3). In this case, *d*-tubocurarine might have sensitized the patient, and specific IgE antibodies against *d*-tubocuraine might have reacted with pancuronium. This possibility could be explored by Prausnitz–Küstner tests or radioimmunoassay (1,4,5). This case might be one of crossed anaphylaxis between *d*-tubocurarine and pancuronium without the involvement of succinylcholine. In fact, the extent of crossed anaphylaxis involving one or more muscle relaxants depends on the patient (1). According to Baldo, the antigenic determinants are quaternary ammonium ions (1). It may be noted that *d*-tubocurarine and pancuronium have two quaternary ammonium ions situated far apart; they are close together in the succinylcholine molecule. This possibly could explain why specific IgE antibodies to *d*-tubocurarine can react with pancuronium and not with succinylcholine.

In conclusion, our feeling is that neither pancuronium nor *d*-tubocurarine should be used for this patient in the future.

D. A. Moneret-Vautrin
*Médicine "D"–Immuno-Allergologie*
*C.H.U. de Nancy-Brabois*
*54511 Vandoeuvre–lès–Nancy Cedex*
*France*

M. C. Laxenaire
*Département d'Anesthésiologie Hôpital Central*
*29 avenue du Maréchal De-Lattre-De Tassigny*
*C.O. No.34–54037 Nancy Cedex*
*France*

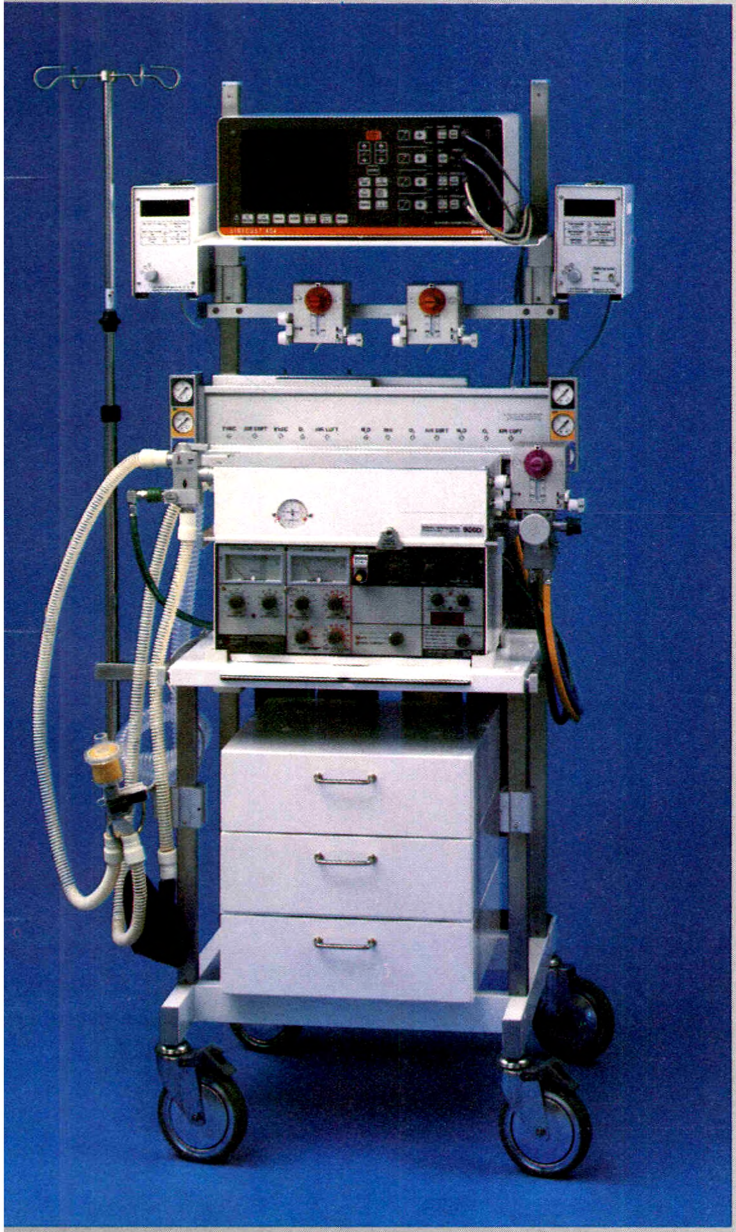
References

1. Baldo BA, Fisher MM. Anaphylaxis to muscle relaxants drugs: cross-reactivity and molecular basis of binding of IgE antibodies detected by radio-immuno-assay. Mol Immunol 1983;20:1393–400.
2. Fisher MM. Anaphylaxis to muscle relaxants: cross-sensitivity between relaxants. Anaesth Intens Care 1980;8:211–3.
3. Vervloet D, Nizankowska E, Arnaud A. Adverse Reactions to suxamethonium and other muscle relaxants under general anesthesia. J Allergy Clin Immunol 1983;6:552–9.
4. Laxenaire MC, Moneret-Vautrin DA, Boileau S, Moeller R. Adverse reactions to intravenous agents in anaesthesia in France. Klin Wochenschr 1982;60:1006–9.
5. Moneret-Vautrin DA, Laxenaire MC, Moeller R. Anaphylaxis due to succinylcholine. Clin Allergy 1981;11:175–83.

**SIEMENS**

Introducing the Servo Anesthesia System

# The advanced anesthesia system for pediatric and adult patients.



Now there's one highly versatile anesthesia system designed for routine and critical care cases involving pediatric as well as adult patients. It's the new Servo Anesthesia System from Siemens. Compact and modular in design, the system is human-engineered for ease of operation and highly accurate control...plus maximum safety.

**New versatility and efficiency in the OR**
The system utilizes our Servo Ventilator, offering the most advanced technology available for both volume-controlled and pressure-supported anesthesia applications. A new ventilation mode, pressure support, enables patients to breathe spontaneously with the assistance of a predetermined pressure. The system continuously monitors all important functions and provides instantaneous readings and audible/visual alarms.

**Advanced monitoring interface**
The Servo Anesthesia System interfaces with a broad range of exclusive, innovative monitoring systems, including the $CO_2$ Analyzer 930, the Lung Mechanics Calculator 940 and the Sirecust 404.

**New ease of maintenance**
You're assured of quality performance with a minimum of maintenance. The system requires only minimal servicing; the costs are extraordinarily low. And best of all, most maintenance is easily performed right on site by members of your own staff. No costly off-site service!

And you're further assured of immediate professional assistance, if necessary, from your Siemens sales and service representatives. It's all part of the Siemens commitment to superior products and systems for healthcare professionals and their patients.

For further information, contact
Siemens-Elema Ventilator Systems,
2360 No. Palmer Dr., Schaumburg,
Illinois 60195—(312) 397-5975, or
call toll-free 1-800-323-1281.

**Siemens...a pioneer in innovative healthcare systems.**

Siemens-Elema Ventilator Systems,
2360 No. Palmer Dr., Schaumburg, IL 60195
☐ Please send me information on Servo Anesthesia System.
Name ______
Institution ______
Address ______
City ______
State ______
Zip ______

MG/5820-009 WLM 174

# Soothing news for busy anesthesiologists

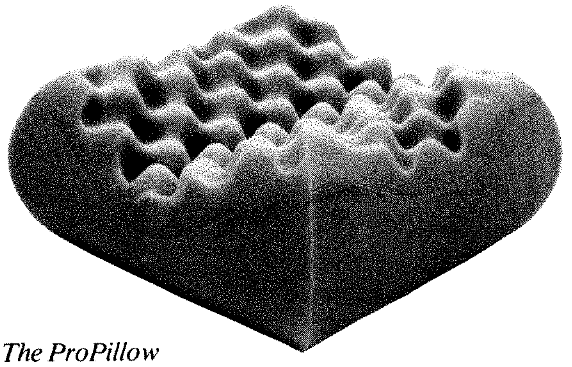
Dr. Smith was having another busy day in surgery. One Swan-Ganz placement had been unusually time-consuming. Plus the patient had been difficult to intubate. To top it off, the pump time had been excessive.

Down the hall, Dr. Jones had a marathon case involving a young woman undergoing a tuboplasty for infertility. Finally, 5½ hours later the surgeons were closing the skin. He heaved a sigh of relief and automatically leveled the table from the previous several hours where the Trendelenberg position had been necessary.

But these two stories don't end here. About 28 days later, *both patients had a bald spot about the size of a silver dollar at the occiput. . . exactly where their heads were resting on the table for hours on end.* They were each advised by their surgeons that they had a 50% chance of their hair growing back within the next year. But there was an equal chance that their hair wouldn't grow back at all. The anesthesiologists on both cases were never told of the problem.

## The ProPillow takes the pressure off

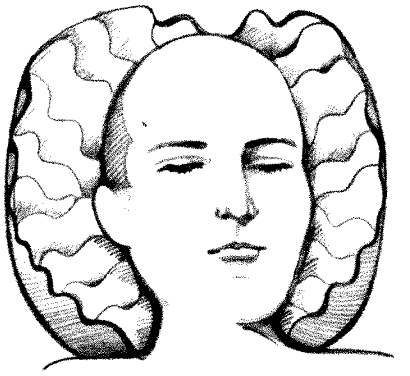
The ProPillow Anesthesia Pillow helps "take off the pressure" to the circulation of the face and scalp during prolonged anesthesia. It's unique "hills and valleys" construction creates a protective effect by evenly distributing the weight of the head and neck. Result: no more pressure in one area greater than any other area. And those precipitous swings in blood pressure are less likely to result in ischemia to the scalp. All this lessens the chance of post-op alopecia.



*The ProPillow Anesthesia Pillow*

## The end of the juggling act

The ProPillow lets you off gracefully from attempts to juggle the heavy head (10 lbs.) during intubation. The ProPillow Anesthesia Pillow stabilizes (by gently gripping) the patient's head in the neutral, "sniffing", position. It even helps free up one of your hands when you're using a mask for short cases.



*The ProPillow Anesthesia Pillow stabilizes the head, supports the neck and helps take the pressure off.*

## An eye for details

Awake patients really appreciate the comfort of the ProPillow Anesthesia Pillow. Especially the eye patients who are undergoing removal of cataracts with intra-ocular lens implants. And the ProPillow fits inside the frame used by Opthalmologists during this tedious microsurgery. Less squirming. . . and possibly sedation required.

## And the price is right

Because of the ProPillow's reasonable price, some say we should call it disposable. But it is made to last for up to 50 cases. You can use a nurse's bouffant cap to cover the ProPillow. Or even spot wash and air-dry it. It's made from a bright blue, breathable, resilient polyurethane foam that's 100% non-allergenic and non-irritating to skin.

It's easy to order the ProPillow Anesthesia Pillow! Call us **TOLL FREE** at **(800) 227-0517 outside California,** or **(800) 554-5541 inside California.** Or, give this page to your head nurse or purchasing agent to get the ProPillow promptly. We ship within 24 hours. *Pediatric Size available, ask for details.

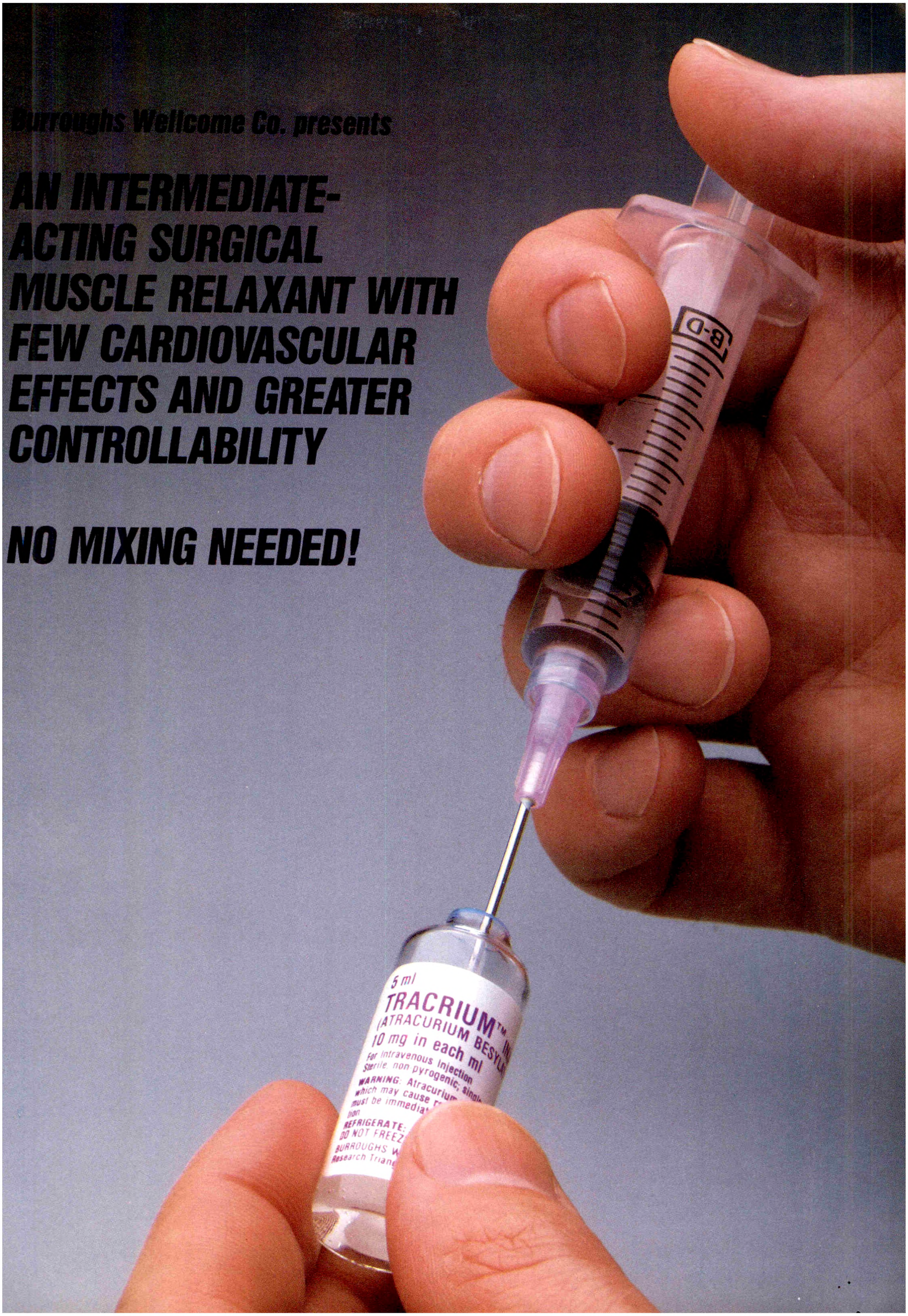
**ProTechPacific**
**1221 Andersen Drive**
**San Rafael, CA 94901**

Makers of the **ProPillow Anesthesia Pillow, NECK-PIL-O Neck Support Pillow, DIXSEY Hip Abduction pillow** and the new **STRAPEZE** *Velcro **Endotracheal Tube stabilizer.**

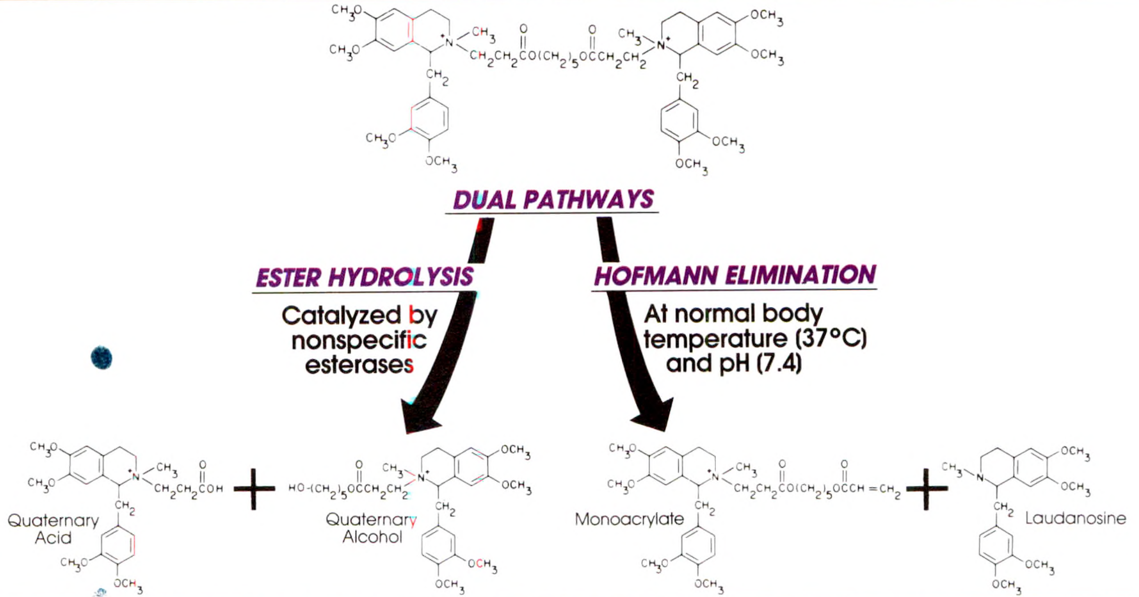
Burroughs Wellcome Co. presents

# AN INTERMEDIATE-ACTING SURGICAL MUSCLE RELAXANT WITH FEW CARDIOVASCULAR EFFECTS AND GREATER CONTROLLABILITY

# NO MIXING NEEDED!



# UNIQUE METABOLISM PROVIDES BETTER PREDICTABILITY, ALLOWING BETTER CONTROL



☐ *Tracrium® Injection (atracurium besylate) is inactivated by two nonoxidative pathways that are not dependent on kidney or liver function:*

1 *Hofmann elimination—a nonenzymatic process that occurs at physiologic temperature and pH*

2 *Ester hydrolysis—catalyzed by nonspecific esterases; normal levels of plasma cholinesterase are not required*

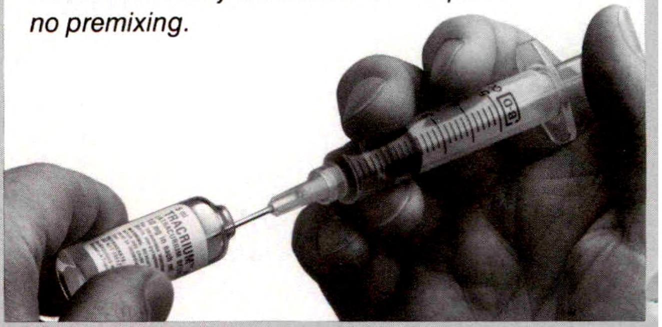
*These attributes make Tracrium a more flexible surgical muscle relaxant—it may be tailored to a wide variety of surgical cases.*

*"Atracurium has the special feature of being broken down to inactive products by the Hofmann elimination reaction. This means that the active drug can be removed from the biophase by other means not totally dependent on enzyme action, redistribution or excretion."[1]*

*"At present, no other available muscle relaxant undergoes this kind of degradation at physiologic pH."[2]*

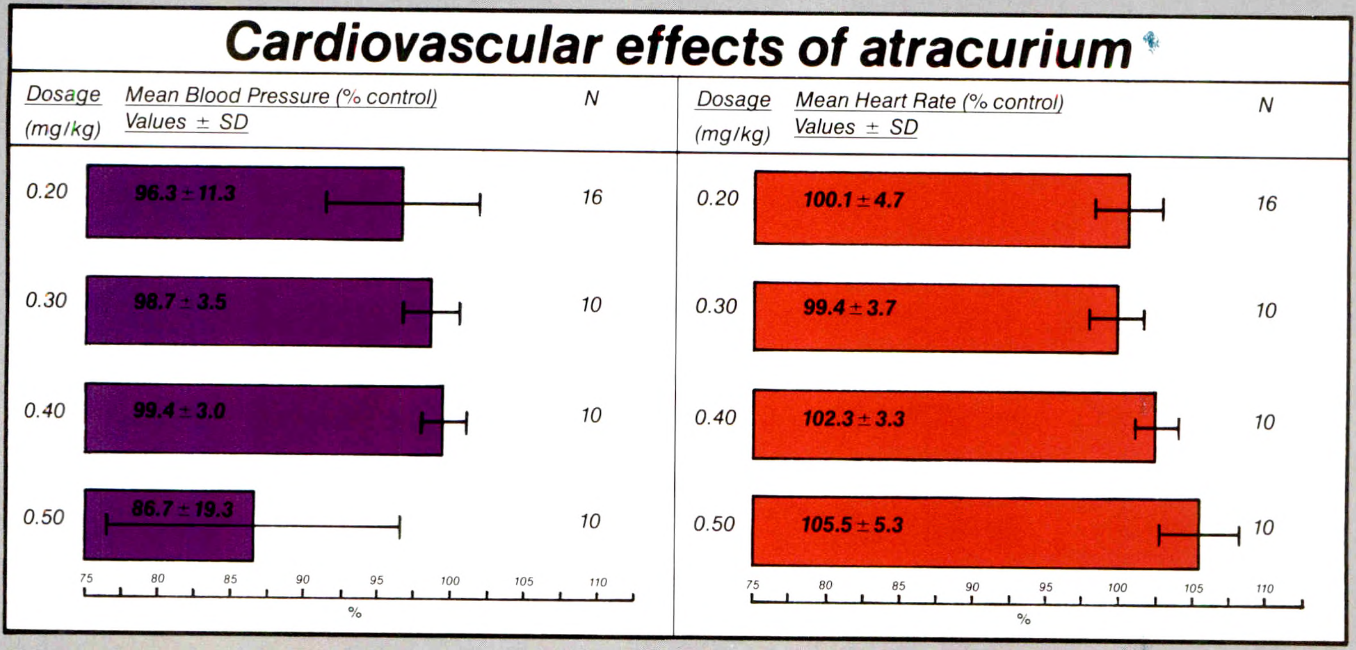
## Convenient and Ready to Use

*Tracrium is easily administered—requires no premixing.*



## Few Cardiovascular Effects at Recommended Dosages

☐ Tracrium® (atracurium besylate) produces virtually no clinically significant cardiovascular hemodynamic changes when administered at recommended dosage levels—a significant benefit in patients with compromised cardiac ability or cardiac risk.



Cardiovascular effects of atracurium

Adapted from Basta et al.[3]

## No Cumulative Effects Upon Recovery, After Multiple Doses

☐ Repeated equipotent doses of Tracrium, administered at equal points of recovery, have no cumulative effect on recovery time

☐ Once recovery begins, it is relatively rapid and independent of dose

☐ This means that you do not have to calculate progressively smaller doses for repeat administration, and that recovery is more consistent and predictable

"One patient received 12 successive doses of atracurium after recovering completely from the initial dose, yet the 25%-75% recovery times were 10.0 and 12.2 min, respectively. This may indicate that atracurium is not cumulative. . . ."[1]

## Minimal Histamine Release

☐ Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine

☐ Clinically significant histamine release occurs well within the clinical dosage range (at $ED_{95}$) for curare, at the upper limits of the clinical dosage range (at 2 × $ED_{95}$) for metocurine and outside the clinical dosage range (at 3 × $ED_{95}$) for atracurium[4]

☐ The lack of hemodynamic changes due to Tracrium suggests minimal histamine release

Please see brief summary of prescribing information on the following page.

REFERENCES:

1. Ali HH, Savarese JJ, Basta SJ, et al: Clinical pharmacology of atracurium: A new intermediate acting nondepolarizing relaxant. Seminars in Anesthesia 1982; 1:57-62.
2. Katz RL, Stirt J, Murray AL, et al: Neuromuscular effects of atracurium in man. Anesth Analg 1982; 61:730-734.
3. Basta SJ, Ali HH, Savarese JJ, et al: Clinical pharmacology of atracurium besylate (BW 33A): A new non-depolarizing muscle relaxant. Anesth Analg 1982; 61:723-729.
4. Basta SJ, Savarese JJ, Ali HH, et al: Histamine-releasing potencies of atracurium besylate (BW 33A), metocurine, and d-tubocurarine. Anesthesiology 1982;57:A261.

Copr. ©1984 Burroughs Wellcome Co. All rights reserved.

**TRACRIUM® INJECTION**
(atracurium besylate)

# TRACRIUM® INJECTION
## (atracurium besylate)

**DESCRIPTION:** Tracrium (atracurium besylate) is an intermediate-duration, nondepolarizing, skeletal muscle relaxant for intravenous administration.

**INDICATIONS AND USAGE:** Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

**CONTRAINDICATIONS:** Tracrium is contraindicated in patients known to have a hypersensitivity to it.

**WARNINGS:** TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

**PRECAUTIONS:**

**General:** Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine. The possibility of substantial histamine release in sensitive individuals must be considered however. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome or other neuromuscular diseases or in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

**Drug Interactions:** The neuromuscular blocking action of Tracrium may be enhanced by enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; or quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

**Pregnancy:** ***Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

**You'll get the latest facts on**
**TRACRIUM® INJECTION**
**(atracurium besylate)**
**at**
**The American Society**
**of Anesthesiologists**
**Annual Meeting**

**San Francisco, CA**
**October 14-16, 1985**

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in children below the age of 2 years have not been established.

**ADVERSE REACTIONS:** Tracrium produced few adverse reactions during extensive clinical trials, most of which were suggestive of histamine release (see PRECAUTIONS section). The overall incidence of clinically important adverse reactions was 7/875 or 0.8%.

In the United Kingdom, where Tracrium has been marketed since December, 1982, the most frequent adverse reactions reported in association with the use of Tracrium are cutaneous histamine-like reactions, bronchospasm, and bradycardia. These have been reported to occur in about one in 10,000 patients. Less frequent adverse reactions are hypotension, heart arrest, tachycardia, cyanosis, and apnea, which have been reported to occur in approximately one in 100,000 patients.

**DOSAGE AND ADMINISTRATION:** Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

A Tracrium dose of 0.4 to 0.5 mg/kg, given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically acceptable neuromuscular blockade under balanced anesthesia generally lasts 20 to 35 minutes; recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

An initial Tracrium dose of 0.3 to 0.4 mg/kg is recommended following the use of succinylcholine for intubation under balanced anesthesia.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg; with halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria. Maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anesthesia, slightly longer under isoflurane or enflurane.

An initial Tracrium dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for patients with significant cardiovascular disease and for patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated.

No Tracrium dosage adjustments are required for patients with renal disease or for pediatric patients two years of age or older. In pediatric patients, maintenance doses may be required with slightly greater frequency than in adults.

**HOW SUPPLIED:** Tracrium Injection, 10 mg atracurium besylate in each ml. Ampuls of 5 ml (50 mg atracurium besylate per ampul). Box of 10 ampuls (NDC-0081-0940-10).

Store under refrigeration at 2° to 8°C (36° to 46°F); DO NOT FREEZE.

U.S. Patent No. 4179507 Printed in U.S.A.

**TRACRIUM® INJECTION**
**(atracurium besylate)**

Wellcome

**Burroughs Wellcome Co.**
Research Triangle Park
North Carolina 27709

84TRA8D

# Five reasons the new Capnogard™ $ETCO_2$ monitor belongs in the OR.

**Sophisticated performance.**

The Capnogard 1250 has all you'd expect from a top-of-the-line end tidal monitor. And more.

Reliably accurate $ETCO_2$, min. $CO_2$, $N_2O$, and respiratory rate displays. Detection and alert of apnea, sample occlusion, and high or low $ETCO_2$ or respiratory rate. Plus a long list of other performance and convenience features.

**Complex electronics make it simple.**

Capnogard's innovative microprocessor control system minimizes operator in-service requirements and ensures reliable, trouble-free operation in the OR. The Capnogard is up and monitoring in less than two minutes. And its self-checking circuitry keeps it that way. Better than just "user friendly," the Capnogard 1250 comes as close to "turn it on and forget it" as you'll find in a sophisticated, multi-function monitor.

**New approaches to traditional $ETCO_2$ measurement problems.**

Calibration and condensation problems have plagued even the best available end tidal monitors. Until now.

Sure, Capnogard is easy to calibrate. But, even better, it has an auto-zeroing system with electronics so stable that gas recalibration is required only twice a year. That's right. The Capnogard gives you six months of accurate monitoring between calibrations.

And instead of wasting time trying to improve the conventional water trap used on other end tidal monitors, Capnogard's designers came up with a dehumidification interface kit with a built-in particulate filter and a semi-permeable tube drying system. Then they added front-panel accessibility to the sample chamber so that it could be cleared in less than a minute right in the OR.

**Unmatched cost effectiveness.**

The Capnogard 1250 is the result of Novametrix' efforts to develop a superbly performing end tidal monitor for the OR with the lowest possible price. You can pay more—even a lot more—for an end tidal unit. But you probably don't need more. And while it's possible to pay a little less for a budget $ETCO_2$ analyzer, you'll end up with a lot less performance.

**It's from Novametrix.**

Critical patient monitoring is Novametrix' only business. And we're proud of our reputation for innovation, reliability, top-notch representatives, and fast, professional service. When the name on the faceplate is Novametrix, you've made an equipment choice you won't regret.

**Get the facts.**

There are more reasons the Capnogard 1250 belongs in *your* OR. Let us fill you in. Write, call our toll-free number, or circle the reply card number for a copy of our comprehensive brochure.

Novametrix Medical Systems, Inc.,
1 Barnes Industrial Park Road,
P.O. Box 690, Wallingford, CT 06492,
(800)243-3444.

NOVAMETRIX

# Anesthesia and Analgesia

## BACK ISSUES AVAILABLE

Available at $3.00 per Issue

| Vol. | Year | Numbers Available | | | | | | Vol. | Year | Numbers Available | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 33 | 1954 | – | 2 | 3 | 4 | 5 | 6 | 41 | 1962 | – | 2 | 3 | – | 5 | 6 |
| 34 | 1955 | 1 | 2 | 3 | 4 | 5 | 6 | 42 | 1963 | – | – | 3 | 4 | 5 | 6 |
| 35 | 1956 | 1 | 2 | 3 | – | 5 | 6 | 43 | 1964 | 1 | – | 3 | – | 5 | 6 |
| 36 | 1957 | – | – | – | – | – | 6 | 44 | 1965 | 1 | 2 | 3 | 4 | 5 | 6 |
| 37 | 1958 | 1 | 2 | 3 | 4 | 5 | 6 | 45 | 1966 | – | 2 | – | 4 | 5 | 6 |
| 38 | 1959 | – | 2 | 3 | 4 | – | 6 | 46 | 1967 | – | 2 | 3 | 4 | – | 6 |
| 39 | 1960 | – | – | 3 | 4 | 5 | 6 | 47 | 1968 | – | – | 3 | 4 | 5 | 6 |
| 40 | 1961 | – | – | – | 4 | 5 | 6 | 48 | 1969 | 1 | 2 | 3 | – | 5 | – |

Available at $4.50 per Issue

| Vol. | Year | Numbers Available | | | | | | Vol. | Year | Numbers Available | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 49 | 1970 | 1 | – | – | – | 5 | 6 | 54 | 1975 | – | 2 | 3 | – | – | 6 |
| 50 | 1971 | 1 | 2 | – | – | – | – | 55 | 1976 | – | 2 | 3 | 4 | 5 | 6 |
| 51 | 1972 | – | 2 | 3 | – | – | 6 | 56 | 1977 | 1 | 2 | 3 | 4 | 5 | 6 |
| 52 | 1973 | 1 | 2 | 3 | 4 | 5 | 6 | 57 | 1978 | 1 | 2 | 3 | 4 | 5 | 6 |
| 53 | 1974 | – | 2 | 3 | 4 | – | – | | | | | | | | |

Available at $5.50 per Issue

| Vol. | Year | Numbers Available | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 58 | 1979 | 1 | 2 | 3 | 4 | 5 | 6 | (only six issues published) | | | | | |
| 59 | 1980 | – | – | 3 | 4 | 5 | 6 | – | 8 | 9 | 10 | 11 | 12 |
| 60 | 1981 | 1 | 2 | 3 | 4 | 5 | 6 | – | – | 9 | 10 | 11 | 12 |
| 61 | 1982 | 1 | 2 | 3 | 4 | 5 | 6 | – | – | 9 | 10 | 11 | 12 |

SINGLE ISSUES PRIOR TO 1954: Write to publisher at address below for listing of issues available at $2.00 each.

OTHER PUBLICATIONS AVAILABLE:

- "Basic and Clinical Physiology of the Liver" (Supplement to Sept.–Oct. 1965 issue)—$3.00.
- Ten-Year (1960–1969) Cumulative Index—$3.00.
- Ten-Year (1970–1979) Cumulative Index—$3.00.
- 1982 (56th Congress) Review Course Lectures—$5.00.
- 1983 (57th Congress) Review Course Lectures—$5.00.
- 1984 (58th Congress) Review Course Lectures—$6.00.

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, Ohio 44122

Please send me the publications circled above, or listed hereunder:

☐ Check for $_______ enclosed.

☐ Please send bill with understanding that ordered material will be sent when payment is received.

Name ____________________________

Address ____________________________

City, State, Zip ____________________________

Requests for single issues beginning with Vol. 62 should be sent to Elsevier Science Publishing Co, Inc., 52 Vanderbilt Avenue, New York, NY 10017.

NYU
Medical
Center

POST-GRADUATE MEDICAL SCHOOL

# ANESTHESIOLOGY COMPREHENSIVE REVIEWS V & VI

## A Unique Approach to Mastery through the Case Discussion Method

**Due to the increasing popularity of this review course** we have scheduled this intensive 5-day program to be repeated twice in 1986.

**MARCH 3-7, 1986**
**Monday-Friday**

**&**

**SEPTEMBER 8-12, 1986**
**Monday-Friday**

These programs will examine in depth the current clinical practice of Anesthesiology with emphasis on recent advances. The entire field of anesthesiology will be covered to provide a comprehensive review to anesthesiologists who wish to refresh their present state of knowledge and clinical practice.

## TOPICS COVERED

Preoperative Evaluation • The Postoperative Period • The Respiratory System • Pediatrics • The Cardiovascular System • Obstetrics • Neuromuscular Relaxants • Sepsis & Shock • Neuro Anesthesia • Aortic and Carotid Surgery • Thoracic Surgery • Anesthesia Equipment • Evoked Potentials • Hyperthermia • Local Anesthetics and Regional Anesthesia • Current Concepts in Pain Management Techniques

FEE: $550   ACCREDITATION: 40 Category I credit hours—AMA

## ANNOUNCING:

**#101 Critical Care for the Anesthesiologist**

A Specialty Review Course, Coming Spring 1986

### Preregistration and Information Form

**#100 Anesthesiology Comprehensive Reviews V and VI**

Please register/send me information for the March ☐   September course ☐
Please send me information on the Critical Care for the Anesthesiologist Course ☐

Name ____________________ Day Phone (   )__________

Address ____________________

Amount Enclosed $__________

**Return to: NYU Post-Graduate Medical School • 550 First Avenue • NY, NY 10016 • (212) 340-5295/24 hour telephone**

AA 9/85

## WEST VIRGINIA UNIVERSITY

Seeking neuroanesthesiologist, pediatric anesthesiologist, and obstetrical anesthesiologist. Academic rank commensurate with credentials. Competitive salary. Applicants must have four postdoctoral years of training, including Clinical Base, Clinical Anesthesia and a Specialized Year. Applicants must have interest in clinical and didactic teaching of residents and medical students. New Hospital under construction. Morgantown is an excellent outdoor recreational community. West Virginia University is an Affirmative Action/Equal Opportunity Employer.

Please reply with resume to:

**Richard W. Eller, M.D., Chairman**
**Department of Anesthesiology**
**WVU Medical Center**
**Morgantown, WV 26506**

---

## ANESTHESIA STAFFING CRISIS

CALL 1-800 FAST GAS (327-8427)
24 HOUR HOT LINE

WORLDWIDE ANESTHESIA ASSOCIATES, INC.

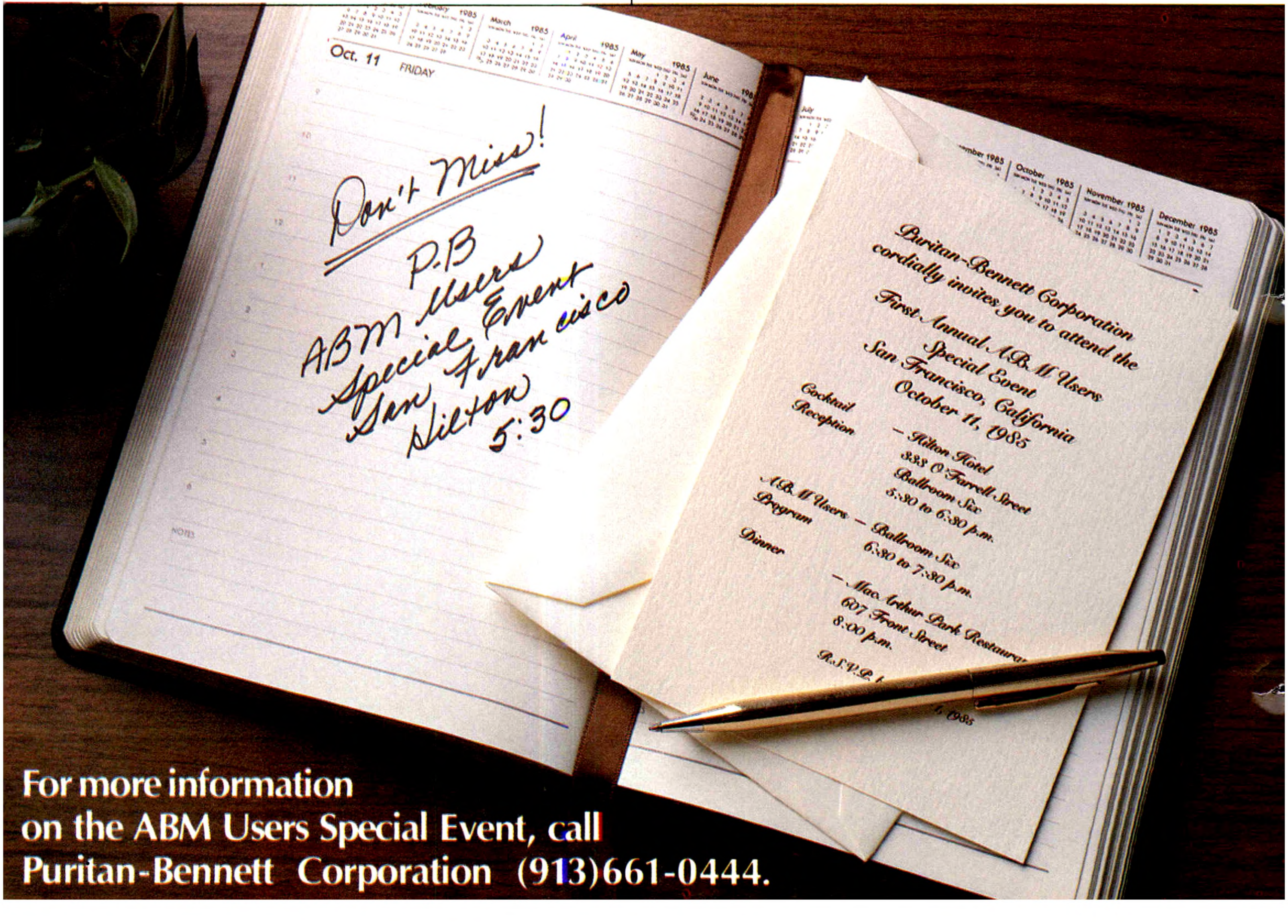
THE NATION'S LARGEST PROVIDER OF PROFESSIONAL ANESTHESIA PERSONNEL

ANESTHESIOLOGISTS • CERTIFIED REGISTERED NURSE ANESTHETISTS • EMERGENCY AND SCHEDULED RELIEF • LOCUM TENENS • CONTRACT MANAGEMENT • PERMANENT RECRUITING •

Worldwide Anesthesia Associates, Inc.

P.O. Box 1547 • UKIAH, CALIFORNIA 95482 • U.S.A.

---



Don't Miss!
P.B
ABM Users
Special Event
San Francisco
Hilton
5:30

Puritan-Bennett Corporation
cordially invites you to attend the
First Annual A.B.M Users
Special Event
San Francisco, California
October 11, 1985

Cocktail Reception — Hilton Hotel
333 O'Farrell Street
Ballroom Six
5:30 to 6:30 p.m.

A.B.M Users Program — Ballroom Six
6:30 to 7:30 p.m.

Dinner — MacArthur Park Restaura
607 Front Street
8:00 p.m.

R.S.V.P.

For more information
on the ABM Users Special Event, call
Puritan-Bennett Corporation (913)661-0444.

# Classified Advertising

**PERMANENT POSITION WANTED**
CRNA—experienced, wishes busy situation, solo or group, best of remuneration. 1-800-521-6750.

**EAST CENTRAL ILLINOIS**
Progressive 210 bed hospital seeking boarded Anesthesiologists. Attractive college town. Average 400 surgeries monthly. Send CV to Bill Rauwolf, SBLHC, Box 372, Mattoon, IL 61938.

**FREELANCE ANESTHETISTS**
Temporary & Permanent—Medical Anesthesiologists—CRNAs/Home based throughout US. If you need an anesthetist call 800-521-6750, ALL-STATES MEDICAL PLACEMENT AGENCY, Box 91, LaSalle, MI 48145 or 313-241-1418 (MI).

**TRANS-AMERICAN ANESTHETISTS, WEST**
Temporary or Permanent MDAs, CRNAs, ready to serve you, up-to-date skills, cooperative, licensed, insured professionals caring about you. Call 800-762-1258, Box 24432, Colorado Springs, CO 80918, or 303/598-2788 (CO).

**ANESTHESIOLOGISTS**
Excellent, prequalified individuals available to join your group on a career or temporary basis. For more information please contact: Southwest Anesthesia Services, PO Box 5719, Santa Fe, New Mexico 87502, (505) 983-7371.

**THE ELLIS FISCHEL STATE CANCER CENTER**
is searching for a Director of Anesthesiology. The director would be expected to provide general and regional anesthesia for all types of cancer surgery. Teaching opportunities are available. Salary is competitive. Contact William G. Kraybill, MD, Chairman of Search Committee for Anesthesiology, Ellis Fischel State Cancer Center, Columbia, MO 65201, or phone 314-875-2214. An equal opportunity employer.

**ROCKY MTS./SOUTHWEST**
We have career and temporary positions available from solo to large group practice in the Rocky Mts. and Southwest. Expenses paid; partnerships usually available. Please contact Southwest Anesthesia Services, R.R. #9 Box 96 MM, Santa Fe, NM 87501. (505) 983-7371.

**ANESTHESIOLOGIST**
Full-time faculty position at Associate/Full Professor level in young department with emphasis on teaching and research. Complete clinical services in one hospital. Prerequisites include: board certified; meet California license requirements; clinical expertise in neuro, pain and/or pediatrics; demonstrated ability as a research scientist and ability to write scholarly articles. Send curriculum vitae, bibliography and names of three references to John H. Eisele, Jr., MD, Anesthesiology Department, University of California, Davis, Medical Center, 2315 Stockton Blvd., Sacramento, CA 95817. Position open until filled, but not later than September 30, 1985. We are an equal opportunity/affirmative action employer.

**LOUISIANA—BOARD CERTIFIED ANESTHESIOLOGISTS**
Louisiana State University School of Medicine in Shreveport has immediate openings for faculty personnel in the Department of Anesthesiology. Academic rank commensurate with education and experience. Excellent financial and fringe benefits offered at all ranks. Shreveport, with a metropolitan area population of 350,000, has a progressive, growing and expanding medical school with an extremely challenging high-risk patient population. An active transplant service is also in operation. Please send curriculum vitae and immediate reply to Norman H. Blass, MD, Professor and Chairman, Department of Anesthesiology, Louisiana State University School of Medicine, 1501 Kings Highway, Shreveport, LA 71130-3932. An affirmative action/equal opportunity employer.

**LOYOLA UNIVERSITY STRITCH SCHOOL OF MEDICINE,**
Maywood, Illinois, located 10 miles from downtown Chicago in the western suburbs. The Department of Anesthesiology is seeking two faculty at the level of assistant or associate professor, depending on experience and academic achievement. Candidates must be board certified with clinical and academic experience and interest in teaching. One position is for a cardiovascular anesthesiologist with experience in invasive monitoring. The second position is for a pediatric anesthesiologist with either board certification in pediatrics or fellowship, and at least 1–2 years of experience in pediatric anesthesia. Faculty rank, salary, and benefits are commensurate with experience. Send curriculum vitae to T.L.K. Rao, MD, Chairman, Department of Anesthesiology, Loyola University, 2160 S. First Avenue, Maywood, IL 60153.

**TUTORING FOR WRITTEN AND ORAL BOARD EXAMS**
Individual or small group sessions given in New York City, San Francisco, and Hawaii. Basic science emphasis. Call 415-321-1117, or reply to Box 1116, Menlo Park, CA 94026.

**CHAIRPERSON—DEPARTMENT OF ANESTHESIOLOGY**
The University of Nebraska College of Medicine is conducting an active search for a Chairperson of Anesthesiology. Applications are sought from board certified individuals with established credentials in research and demonstrated leadership in education. Interested applicants should submit a curriculum vitae by October 15, 1985, to Leon F. Davis, DDS, MD, Office of the Dean, University of Nebraska College of Medicine, 42nd Street and Dewey Avenue, Omaha, Nebraska 68105. The University of Nebraska is an affirmative action/equal opportunity employer.

**TEXAS ANESTHESIOLOGIST**
Director of Cardiac Anesthesiology programs at The University of Texas Health Science Center at San Antonio. Established academic anesthesiologist required. Please send inquiries and curriculum vitae to R. Brian Smith, MD, Professor and Chairman, Department of Anesthesiology, The University of Texas Health Science Center, 7703 Floyd Curl Dr., San Antonio, TX 78284. Equal opportunity employer.

**CLASSIFIED ADS**

*Anesthesia and Analgesia* makes available classified advertising space for those interested in obtaining positions, or wishing to announce meetings, postgraduate courses, or other events. Display space (minimum ¼ page) is also available through Pharmaceutical Media, Inc. Rates for classified advertising: $.90 per word, minimum twenty words; box number ads $1.00 per word. Copy deadline 7 weeks prior to publication, e.g., for the March issue, copy should be received by the 1st of January. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. Ad copy, subject to acceptance by publisher, should be mailed to:

*Anesthesia and Analgesia*
Desk Editorial
Classified Ads
Elsevier Science Publishing Co. Inc.
52 Vanderbilt Avenue, New York, NY 10017.

Make checks payable to Elsevier Science Publishing Co, Inc.

**ANESTHESIOLOGIST**
To join a group of anesthesiologists and anesthetists in a college town in the Northeast. One and one-half hours from a large city. No open heart or neurosurgery. Nearby skiing, hunting, and fishing. Immediate opening, but will wait for suitable candidate. Send CV and references to Box F20, ℅ *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

**NEW ENGLAND SEA COAST**
Group of anesthesiologists in medium-sized community hospital seek partner. Must be B/C (or B/E with fellowship). All surgeries except cardiac. Sea coast area of New England; easy access to recreational and cultural activities. Reply with CV to Box G16, ℅ *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

**CENTRAL MARYLAND**
Opportunity for BC/BE Anesthesiologist. Good location. Minimum call. Send CV to Box F21, ℅ *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

**ANESTHESIOLOGIST NEEDED**
BE/BC. Young staff, progressive hospital on beautiful shores of Western Michigan. All types of surgery except open-heart, no OB. Experience in pain management required. Salary negotiable. Send CV to M.J. Kilbride, DO, Muskegon General Hospital, 1700 Oak Avenue, Muskegon, MI 49442.

**UTAH**
The University of Utah seeks an anesthesiologist who is board certified in anesthesiology, preferably with a PhD in physiology or pharmacology for a position at the level of Assistant Professor. Candidates should be qualified in clinical care, have previous teaching experience, and be capable of independent basic science research. Send curriculum vitae to K.C. Wong, MD, Chairman, Department of Anesthesiology, University of Utah, College of Medicine, 50 North Medical Drive, Salt Lake City, Utah 84132. Equal opportunity/affirmative action employer.

**IV INFUSION DOSES WHEN YOU NEED THEM.**
Trim chart provides preparation and drip rates for 15 vasoactive and anesthetic drugs in durable pocket-size format. Send $3.50 and self-addressed stamped envelope to Heartcard Products, 10849 Deborah Drive, Potomac, MD 20854.

**THE UNIVERSITY OF COLORADO HEALTH SCIENCES CENTER**
is seeking qualified candidates for the position of CHAIRMAN, Department of Anesthesiology. Please submit nominations or applications with vitae by October 15 to Dr. T.N. Evans, University of Colorado Health Sciences Center, 4200 East Ninth Avenue, PO Box B198, Denver, CO 80262. The University of Colorado is an equal opportunity/affirmative action employer.

**UTAH**
The University of Utah seeks an anesthesiologist who is board certified/eligible in anesthesiology and who has completed a formal fellowship in pain. Opportunity to do clinical anesthesia, pain management, and research. Competitive academic salaries at the Instructor level. Send curriculum vitae to K.C. Wong, MD, Chairman, Department of Anesthesiology, University of Utah, College of Medicine, 50 North Medical Drive, Salt Lake City, UT 84132. Equal opportunity/affirmative action employer.

**POSITION NOW AVAILABLE**
for board certified/eligible anesthesiologist to join three-member incorporated group with CRNAs in a very progressive community hospital. All types of procedures except open heart. Send CV to Box F23, ℅ *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

**PRIVATE TUTORING AVAILABLE FOR WRITTEN AND ORAL BOARD EXAMS**
Send name, address, and phone to Box ANA 5-84-E, ℅ *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Co., Inc., 52 Vanderbilt Avenue, New York, NY 10017.

**ANESTHESIOLOGIST**
Board certified anesthesiologist, 3–5 years experience for busy mid-west practice in 700-bed hospital. Send CV to Box H19, ℅ *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

**WORLDWIDE ANESTHESIA**
is an exciting organization of anesthesiologists and CRNAs who specialize in relief services and provide qualified candidates for permanent positions throughout the US. To be included in our computerized data base or to recruit from the nation's largest resources of anesthesia personnel, call or write Worldwide Anesthesia, Box 1547, Ukiah, CA 95482. Nationwide 1-800-327-8427. "Over a decade of placement experience."

**MISSOURI**
200-bed university pediatric hospital; 200 CV anesthetics/yr. 5500 anesthetics/yr. Full-time university faculty position includes malpractice, life, disability, and health insurance and retirement fringe benefits. Minimum: one year fellowship in pediatric anesthesia. Send CV to John F. Schweiss, MD, Professor and Chairman, Department of Anesthesiology, St. Louis University School of Medicine, 1325 South Grand Boulevard, St. Louis, MO 63104.

**ANESTHESIOLOGIST**
to join a group of anesthesiologists and anesthetists in a college town in the Northeast. One and one-half hours from a large city. No open heart or neurosurgery. Nearby skiing, hunting, and fishing. Immediate opening, but will wait for suitable candidate. Send CV and references to Box F20, ℅ *Anesthesia and Analgesia*, Desk Editorial, 52 Vanderbilt Avenue, New York, NY 10017.

**OKLAHOMA: ANESTHESIOLOGIST**
DO, BE/BC. To join group of 2, DO anesthesiologists, no CRNAs, in challenging practice encompassing all types of anesthesia except open heart. Reply to Box F22, ℅ *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

KING SAUD UNIVERSITY
COLLEGE OF MEDICINE
RIYADH, SAUDI ARABIA

CARDIAC ANAESTHESIOLOGISTS

Applications are invited from suitably qualified anaesthesiologists to fill the posts of Consultants, Senior Registrars, and Registrars in the Cardiac Surgery Unit projected to open in June 1986, at King Khalid University Hospital.

Applicants should have American Board with two years experience in Cardiac Anaesthesia or other equivalent qualification.

Very attractive and negotiable salaries.

Application letter with comprehensive curriculum vitae and addresses of three references should be sent to:

The Dean, College of Medicine
King Saud University
P.O. Box 2925
Riyadh 11461, Saudi Arabia

---

**10th CARIBBEAN SYMPOSIUM IN ANESTHESIOLOGY AND RELATED FIELDS**

**DECEMBER 4–8, 1985**
**CARIBE HILTON HOTEL**
**SAN JUAN, PUERTO RICO**

***"THE SUBSPECIALTIES OF ANESTHESIOLOGY"***

For information write:

Miguel Colón-Morales, M.D.
G.P.O. Box 4547
San Juan, Puerto Rico 00936
(809) 758-9200

---

**The Department of Anesthesiology and The Page and William Black Post-Graduate School of Medicine of the Mount Sinai School of Medicine (CUNY)**

***announce***

**The 23rd Bernard H. Eliasberg Memorial Symposium**

**CARDIOVASCULAR PHARMACOLOGY**

**Saturday and Sunday, November 23 and 24, 1985**

**Mount Sinai Medical Center, New York, New York**

Guest Faculty: E. I. Eger II, M.D., Elizabeth A. M. Frost, M.D., Carl E. Rosow, M.D., Ph.D., Peter Rothstein, M.D., Edmund H. Sonnenblick, M.D., Harry Wollman, M.D.; Mount Sinai School of Medicine Faculty: James B. Eisenkraft, M.D., Berry I. Feinberg, M.D., Randall B. Griepp, M.D., Joel A. Kaplan, M.D., Joel Kupersmith, M.D., Kenneth LaMantia, M.D., John Manos, M.D., Raymond Miller, M.D., K. P. Rentrop, M.D., George Silvay, M.D., Ph.D., Daniel Thys, M.D.

*The Page and William Black Post-Graduate School of Medicine of the Mount Sinai School of Medicine (CUNY) designates this continuing medical education activity for 11 hours in Category I of the Physician's Recognition Award of the American Medical Association.*

For further details contact:

**George Silvay, M.D., Ph.D., Department of Anesthesiology**
**Mount Sinai Medical Center, One Gustave L. Levy Place,**
**New York, New York 10029**
**(212) 650-5954**

Elsevier Introduces
Men and Women Who Paved the Way for Modern-Day Neurosurgeons –

**Neurosurgical Giants: Feet of Clay and Iron**

**Paul C. Bucy, M.D.**, founder and editor of *Surgical Neurology*, Professor Emeritus of Surgery (Neurosurgery), Northwestern University Medical School, Chicago, Illinois; and Clinical Professor Emeritus, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina.

The pioneers of neurological surgery were more than ordinary men and women: they were risk-takers of great determination and strength with universal human weaknesses. Their successes and failures constitute the history of neurological surgery.

***Neurosurgical Giants: Feet of Clay and Iron*** presents the biographies of the extraordinary men and women who advanced the scope and integrity of neurological surgery from its beginning in 1879 to the present.

The imagination, courage, and foibles are here in the life stories of more than sixty of this field's outstanding pioneers. Almost all of the surgeons mentioned were known to the editor, who includes some of his own pithy comments.

For students of neurology and neuroscience, and neurosurgeons interested in the backgrounds and characters of the men and women who shaped their specialty, this publication is an excellent, informative, and unique source.

1984 461 pages 0-444-009396 cloth $65.00
(Dfl. 210.00 outside North America)

Order from your usual supplier or **In North America:**
Elsevier Science Publishing Co., Inc., P.O. Box 1663,
Grand Central Station, New York, NY 10163
**in the rest of the world:**
Elsevier Science Publishers, P.O. Box 211, 1000 AE
Amsterdam, The Netherlands

**Note:** Price subject to change without notice. In NY State, please add applicable sales tax.

EB256

Elsevier

# INDEX TO ADVERTISERS

- American Critical Care
  - *Hespan* . . . . . . . . . . A6, A7, A8
- Anaquest
  - *Forane* . . . . . . . . . . A9 thru A12
- Bard Critical Care
  - *Institutional* . . . . . . . . . . A28, A29
- Breon Laboratories
  - *Marcaine* . . . . . . . . . . A37, A38
- Burroughs Wellcome Co.
  - *Tracrium* . . . . . . . . . . A45 thru A48, Cover 4
- Carribean Symposia in Anesthesiology & Related Fields
  - *Continuing Education* . . . . . . . . . . A55
- Classified Advertising . . . . . . . . . . A53, A54
- Elkins-Sinn, Inc.
  - *Duramorph PF* . . . . . . . . . . A39 thru A42
- Halocarbon Laboratories
  - *Halothane* . . . . . . . . . . A27
- Janssen Pharmaceutica
  - *Inapsine* . . . . . . . . . . A16, A17
  - *Sufenta* . . . . . . . . . . A32, A33, A34
- King Saud University
  - *Employment Opportunities* . . . . . . . . . . A55
- Mount Sinai School of Medicine
  - *Continuing Education* . . . . . . . . . . A55
- Nellcor, Inc.
  - *Pulse Oximeter* . . . . . . . . . . A14, A15
- Novametrix Medical Systems, Inc.
  - *Capnogard 1250* . . . . . . . . . . A49
- NYU Post Graduate Medical School
  - *Continuing Education* . . . . . . . . . . A51
- Olympus Medical
  - *LF-1* . . . . . . . . . . A21, A22
- Organon Pharmaceuticals
  - *Norcuron* . . . . . . . . . . Cover 2, A1, A2
  - *Pavulon* . . . . . . . . . . A58, Cover 3
- ProTech Pacific
  - *ProPillow* . . . . . . . . . . A44
  - *Strapeze* . . . . . . . . . . A23
- Puritan-Bennett Corp.
  - *Institutional* . . . . . . . . . . A52
- Reichert-Fiber Optics
  - *Flexible Laryngoscope* . . . . . . . . . . A13
- Hoffman La Roche, Inc.
  - *Injectable Valium* . . . . . . . . . . A24, A25, A26
- Siemens Corporation
  - *Servo Anesthesia System* . . . . . . . . . . A43
- Siemens-Elema AB
  - *Servo Ventilator* . . . . . . . . . . A18, A19
- Traverse Medical Monitors
  - *Capnometer* . . . . . . . . . . A35
- West Virginia University
  - *Employment Opportunities* . . . . . . . . . . A52
- Worldwide Anesthesia Associates, Inc.
  - *Employment Opportunities* . . . . . . . . . . A52

*Advertising Office:* Pharmaceutical Media, Inc., 130 Madison Avenue, 6th Floor, New York 10016. Telephone: (212) 685-5010

## IARS REVIEW COURSE LECTURES AVAILABLE

____ 1984, 58th Congress—24 Review Course Lectures—$6.00

____ 1983, 57th Congress—16 Review Course Lectures—$5.00

____ 1982, 56th Congress—14 Review Course Lectures—$5.00

To:
International Anesthesia Research Society
3645 Warrensville Center Road
Cleveland, Ohio 44122

Please send Lecture Booklets checked above.

My check, payable to IARS in the amount of
$ ________ is enclosed.

________________________________
(Name)

________________________________
(Mail Address)

________________________________

________________________________
(City, State, Zip)

---

**PAVULON®**
(pancuronium bromide, injection)

**BRIEF SUMMARY**
**(Please consult package insert for full prescribing information.)**

THIS DRUG SHOULD ONLY BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS

**ACTIONS:** Pavulon is a non-depolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform) on the myoneural junction.

Pavulon (pancuronium bromide) is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether enflurane and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, clindamycin, kanamycin, gentamicin and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

**CONTRAINDICATIONS:** Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion

**WARNINGS:** PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS, WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION

In patients who are known to have myasthenia gravis small doses of Pavulon may have profound effects. A peripheral nerve stimulator is especially valuable in assessing the effects of Pavulon in such patients.

**USAGE IN PREGNANCY:** The safe use of pancuronium bromide has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards

Pavulon may be used in operative obstetrics (Cesarean section), but reversal of pancuronium may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy, because magnesium salts enhance neuromuscular blockade. Dosage should usually be reduced, as indicated, in such cases.

**PRECAUTIONS:** Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

**ADVERSE REACTIONS:** Neuromuscular: the most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: A slight increase in pulse rate is frequently noted.

Gastrointestinal: Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of Pavulon.

Respiratory: One case of wheezing, responding to deepening of the inhalational anesthetic, has been reported.

**DRUG INTERACTION:** The intensity of blockade and duration of action of Pavulon is increased in patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane.

Prior administration of succinylcholine, such as that used for endotracheal intubation, enhances the relaxant effect of Pavulon and the duration of action. If succinylcholine is used before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows signs of wearing off.

**DOSAGE AND ADMINISTRATION:** Pavulon should be administered only by or under the supervision of experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. See package insert for suggested dosages.

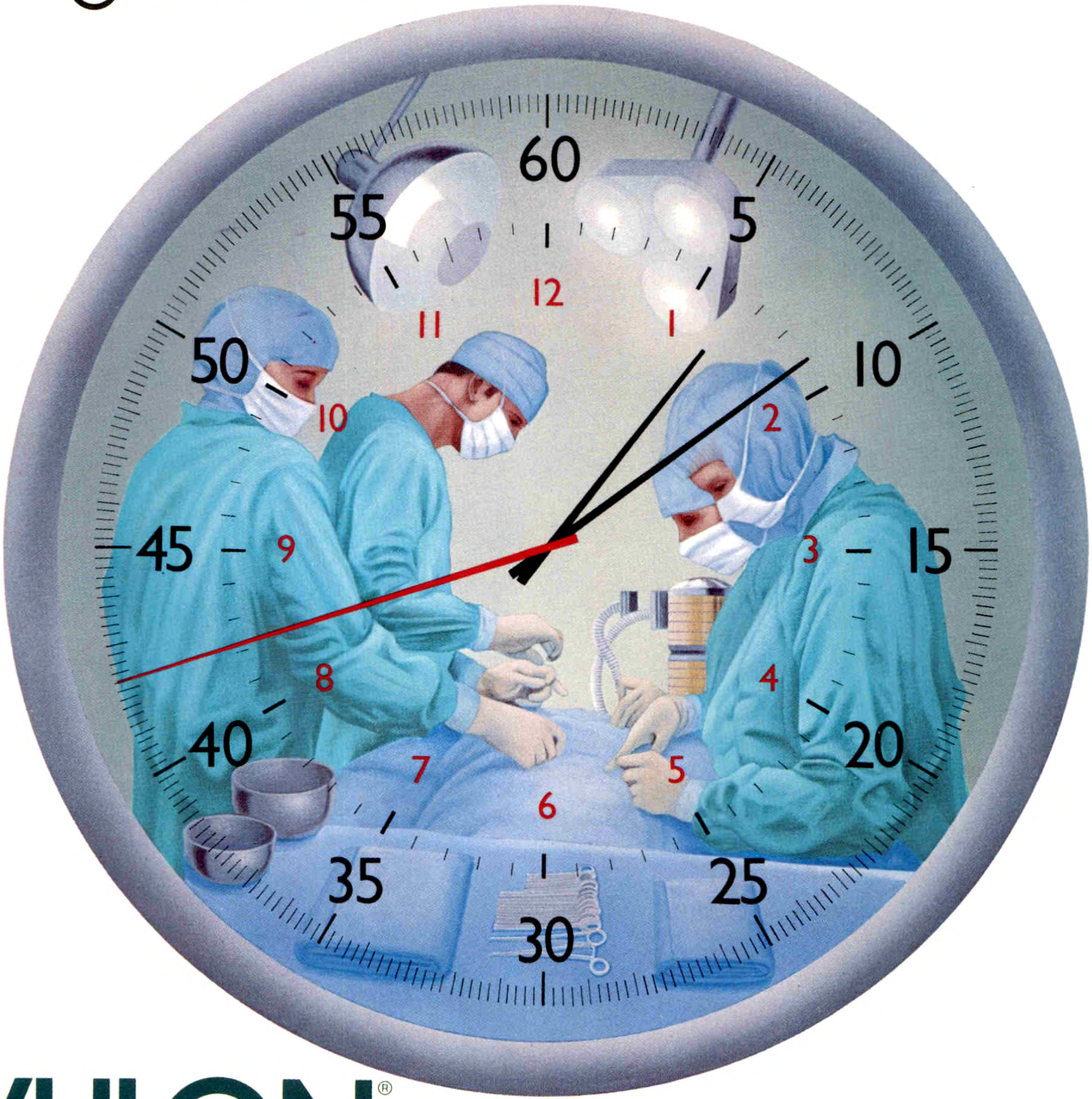
**CAUTION:** Federal law prohibits dispensing without prescription.

**HOW SUPPLIED:**
2 ml. ampuls–2 mg./ml.–boxes of 25, NDC #0052-0444-26
5 ml. ampuls–2 mg./ml.–boxes of 25, NDC #0052-0444-25
10 ml. vials–1 mg./ml.–boxes of 25, NDC #0052-0443-25

Organon
**Organon Pharmaceuticals**
A Division of Organon Inc.
West Orange, N.J. 07052

OR-5089

Because the longer procedure raises the surgical risk...



**PAVULON®**

(pancuronium bromide injection)

Your best choice for 60-plus minutes of dependable relaxation... in every type of patient

Organon

**Organon Pharmaceuticals**
A Division of Organon Inc.
West Orange, N.J. 07052

Please see preceding page for brief summary of prescribing information.

# ANNOUNCING: The new, easily identifiable, economical, shatter-resistant, 10 ml, multiple-dose vial

**(100 mg atracurium besylate per vial).**

Multiple-dose vials can reduce the amount of Tracrium subject to waste by as much as 22% when compared to ampules!*

*Data on file, Burroughs Wellcome Co.

**TRACRIUM® INJECTION**
(atracurium besylate)

Wellcome

**Burroughs Wellcome Co.**
Research Triangle Park
North Carolina 27709

Copr. © 1985 Burroughs Wellcome Co. All rights reserved. 85TRA10

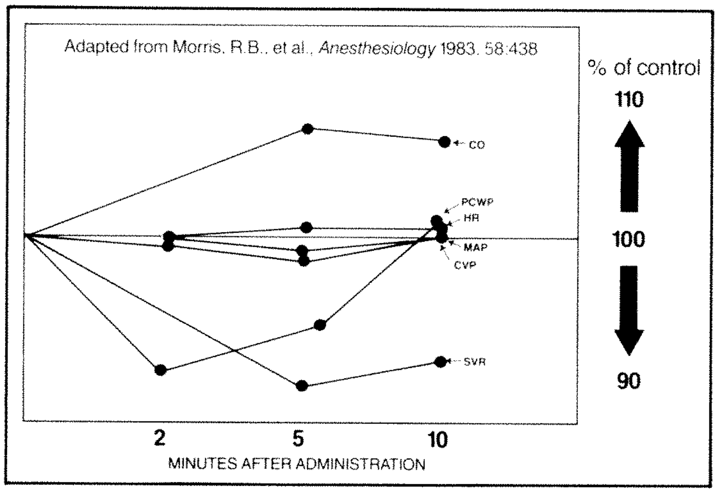
ISSN 0003-2999
Volume 64, Number 10, October 1985

Acc.
9.12.86

# Anesthesia and Analgesia

**Journal of the International Anesthesia Research Society**
Oldest Publication in the Specialty—Established 1922

# In neuromuscular blockade…
# Closest to the ideal:


Adapted from Morris, R.B., et al., *Anesthesiology* 1983, 58:438

## Free of clinically significant cardiovascular effects

NORCURON is the only surgical muscle relaxant for which no clinically significant adverse cardiovascular effects have been observed in clinical trials.[1-3] This makes NORCURON unique among all neuromuscular blocking agents in clinical use.[4]

The Effect of Non-depolarizing Muscle Relaxants on Histamine Levels, Mean Arterial Pressure and Heart Rate[5]

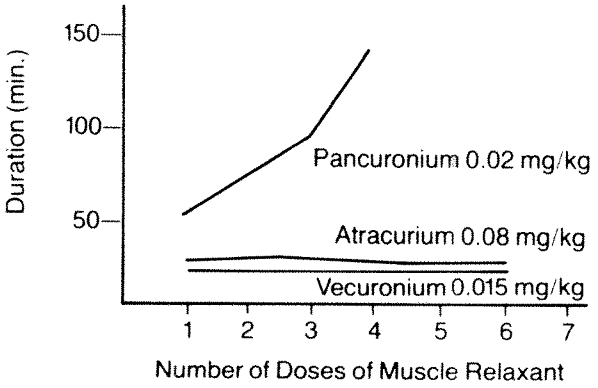
| | | | Percent of Control | | |
|---|---|---|---|---|---|
| Drug | Dose (mg/kg) | $xED_{95}$ | Histamine | Mean Arterial Pressure | Heart Rate |
| tubocurarine | 0.5 | 1 | 318 | 78 | 116 |
| metocurine | 0.5 | 2 | 212 | 79 | 119 |
| atracurium | 0.6 | 3 | 192 | 80 | 108 |
| vecuronium | 0.1 | 1.7 | 117 | 100 | 99 |
| vecuronium | 0.2 | 3.5 | 87 | 99 | 102 |

## Histamine release unlikely to occur

Histamine release has not been observed with NORCURON…as shown by preliminary clinical experience. In doses up to 3.5 times the $ED_{95}$, it causes no increase in circulating histamine nor does it decrease systemic blood pressure.[5]

Hypotension and tachycardia tend to occur when histamine levels are increased to about 200% of control.[5]

The Neuromuscular Effects of Maintenance Doses of Vecuronium, Atracurium and Pancuronium[6,7]



## No clinically significant cumulative effects seen

With NORCURON cumulative effects are not seen in clinical practice. The interval between repeated doses has been found to remain constant between as many as six to ten repeated administrations.[6,7]

# NORCURON®

## (vecuronium bromide for injection)

Safety Index and Comparative Safety Ratios[8]

$$\text{Safety Index} = \frac{ED_{50} \text{ autonomic inhibition}}{ED_{95} \text{ neuromuscular blockade}}$$

Comparative Safety Ratios

| For Vagolytic Effects | | For CV/Histamine Related Effects | |
|---|---|---|---|
| gallamine | 1:1 | d-tubocurarine | 1:1 |
| pancuronium | 3:1 | metocurine | 2:1 |
| atracurium | 25-30:1 | atracurium | 3:1 |
| vecuronium | 60:1 | vecuronium | * |

*cannot be calculated since it does not cause any CV or histamine related effects

## Outstanding safety profile

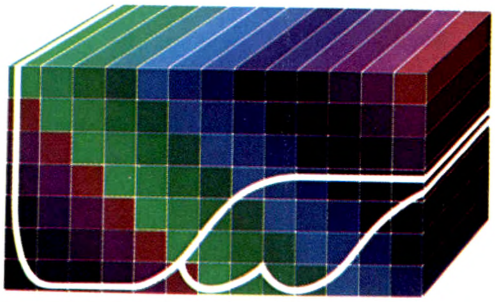
The Safety Index helps quantify the improved safety of the newer muscle relaxants on a relative basis. The characteristics of cardiovascular effects and histamine release are areas where the new agents, particularly NORCURON, have made the most significant gains.[8]

The Safety Index is described as the $ED_{50}$ for autonomic inhibition over the $ED_{95}$ for neuromuscular blockade.[8]

A Comparison of Surgical Muscle Relaxants vs. The Ideal[4]
(" + " signifies proximity to the ideal)

| Characteristic | Vecuronium | Atracurium | Pancuronium | Succinylcholine | D-tubocurarine |
|---|---|---|---|---|---|
| Onset of Action | – | – | – | + | – |
| Histamine Release | + | – | + | + | – |
| Cardiovascular Side Effects | + | + / – | – | – | – |
| Duration of Action | + | + | – | + | – |
| Cumulative Effects | + | + | – | – | – |
| Rate of Recovery | + | + | – | + | – |
| Reversibility | + | + | + | – | + |
| Potency | + | + | + | – | – |
| Non-depolarizing | + | + | + | – | + |
| Metabolite Activity | + | +* | + | + | + |

*Currently under evaluation.



**NORCURON®**
(vecuronium bromide for injection)

## Closest to the ideal

Of the newer short- to intermediate-acting drugs, NORCURON has the most ideal profile, specifically attributable to its outstanding safety features relating to cardiovascular side effects and histamine-releasing properties.[4]

Organon

**References**

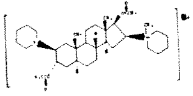
**1.** Durant NN: Norcuron®—A new non-depolarizing neuromuscular blocking agent. *Semin Anesth* 1:47-56, 1982. **2.** Morris RB, Cahalan MK, Miller RD, et al: Cardiovascular effects of vecuronium (ORG NC45) and pancuronium in patients undergoing coronary artery bypass grafting. *Anesthesiology* 58:438-440, 1983. **3.** Krieg N, Crul JF, Booij LH: Relative potency of ORG NC45, pancuronium, alcuronium, and tubocurarine in anaesthetized man. *Br J Anesth* 52:783-787, 1980. **4.** Miller RD (ed): *Innovations in Surgical Muscle Relaxants.* Far Hills, NJ, Gardiner-Caldwell Synermed, 1984. **5.** Basta SA, Savarese JJ: Comparative histamine-releasing properties of vecuronium, atracurium, tubocurarine and metocurine, in Agoston S, et al (eds): *Clinical Experiences with Norcuron (ORG NC45, vecuronium bromide).* Amsterdam, Excerpta Medica, 1983, p. 183. **6.** Foldes FF, et al: Muscular relaxation with atracurium, vecuronium and Duodor under balanced anaesthesia. *Br J Anaesth* 55 (suppl. 1): 97S, 1983. **7.** Fahey MR, Morris RB, Miller RD, et al: Clinical pharmacology of ORG NC45 (Norucon®): a new non-depolarizing muscle relaxant. *Anesthesiology* 55:6, 1981. **8.** Clinical Courier, Vol. 2, No. 4, July 1984.

# NORCURON® (NC-45)

Vecuronium Bromide for Injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

**DESCRIPTION:** NORCURON® (vecuronium bromide for injection) is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[(2β, 3α, 5α, 16β, 17β)-3, 17-bis (acetyloxy)-2-(1-piperidinyl) androstan-16-yl]-1-methyl-, bromide. The structural formula is:



Norcuron® is supplied as a sterile freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Following reconstitution with solvent (water for injection) the resultant solution is isotonic and has a pH of 4. Each 5 ml vial contains 10 mg vecuronium bromide. Each vial also contains citric acid, dibasic sodium phosphate, sodium hydroxide, and/or phosphoric acid to buffer and adjust pH and mannitol to make isotonic.

**CLINICAL PHARMACOLOGY:** Norcuron® (vecuronium bromide for injection) is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron® is about 1/3 more potent than pancuronium; the duration of neuromuscular blockade produced by Norcuron® is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The $ED_{90}$ (dose required to produce 90% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron® dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3.0 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron® is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron® is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron® (vecuronium bromide for injection) may be decreased by approximately 15% (see Dosage and Administration Section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron®, the administration of Norcuron® should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron® has not been studied (see Drug Interactions).

Repeated administration of maintenance doses of Norcuron® has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to a 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron® neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started the neuromuscular block produced by Norcuron® (vecuronium bromide for injection) is readily reversed with various anticholinesterase agents, e.g. pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. There have been no reports of recurarization following satisfactory reversal of Norcuron® induced neuromuscular blockade; rapid recovery is a finding consistent with its short elimination half-life.

**Pharmacokinetics:** At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron® is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery. In late pregnancy, elimination half-life may be shortened to approximately 35-40 minutes. The volume of distribution at steady state is approximately 300-400 ml/kg; systemic rate of clearance is approximately 3-4.5 ml/minute/kg. In man, urine recovery of Norcuron® varies from 3-35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged Norcuron® has been detected in human plasma following clinical use. One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of the injected dose; 3-deacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron® (vecuronium bromide for injection); equipotent doses are of approximately the same duration as Norcuron® in dogs and cats. Biliary excretion accounts for about half of the dose of Norcuron® within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron®. Limited data derived from the patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron® in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary-capillary-wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease.) Limited clinical experience (3 patients) with use of Norcuron® during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron® (vecuronium bromide for injection) has no clinically significant effects on hemodynamic parameters and will not counteract those hemodynamic changes or known side effects produced by or associated with anesthetic agents.

Preliminary data on histamine assay in 16 patients and available clinical experience in more than 600 patients indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

**INDICATIONS AND USAGE:** Norcuron® is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

**CONTRAINDICATIONS:** None known.

**WARNINGS:** NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

**PRECAUTIONS:**

**Renal Failure:** Norcuron® (vecuronium bromide for injection) is well-tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

**Altered Circulation Time:** Conditions associated with slower circulation time in cardiovascular disease, old age, or edematous states resulting in increased volume of distribution may contribute to a delay in onset time; therefore dosage should not be increased.

**Hepatic Disease:** Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in recovery from Norcuron® metabolism and excretion (see Pharmacokinetics). Data currently available do not permit dosage recommendations in patients with impaired liver function.

UNDER THE ABOVE CONDITIONS, USE OF A PERIPHERAL NERVE STIMULATOR FOR ADEQUATE MONITORING OF NEUROMUSCULAR BLOCKING EFFECT WILL PRECLUDE INADVERTENT EXCESS DOSING.

**Severe Obesity or Neuromuscular Disease:** Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron® (vecuronium bromide for injection).

**Malignant Hyperthermia:** Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia.

**Drug Interactions:** Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see CLINICAL PHARMACOLOGY).

The use of Norcuron® (vecuronium bromide for injection) before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied. Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®; therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

**Inhalational Anesthetics:** Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane.

With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see CLINICAL PHARMACOLOGY).

**Antibiotics:** Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce a neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin, polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron® (vecuronium bromide for injection) during surgery, unexpected prolongation of neuromuscular block should be considered a possibility.

**Other:** Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance neuromuscular blockade.

**Drug/laboratory test interactions:** None known.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

**Pregnancy: Pregnancy Category C:** Animal reproduction studies have not been conducted with Norcuron®. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

**Pediatric Use:** Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® (vecuronium bromide for injection) on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

**ADVERSE REACTIONS:** Norcuron® was well-tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade, although not yet reported, is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

**OVERDOSAGE:** There has been no experience with Norcuron® overdosage. The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation. Excessive doses of Norcuron® (vecuronium bromide for injection) can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade and help to differentiate residual neuromuscular blockade from other causes of decreased respiratory reserve. Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide injection), neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

**DOSAGE AND ADMINISTRATION:** Norcuron® (vecuronium bromide for injection) is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

To obtain the maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the $ED_{90}$) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3.0 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® (vecuronium bromide for injection) is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained (see CLINICAL PHARMACOLOGY).

**Dosage in children:** Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year o age but older than 7 weeks are moderately more sensitive to Norcuron® (vecuronium bromide for injection) on a mg/kg basis than adults and take about 1½ times as long to recover. See also sub-section of PRECAUTIONS titled Pediatric use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS).

**COMPATIBILITY:** Norcuron® is compatible in solution with

| | |
|---|---|
| 0.9% NaCl solution | 5% glucose in saline |
| 5% glucose in water | Lactated Ringers |

**HOW SUPPLIED:** 5 ml vials (contains 10 mg of active ingredient) and 5 ml ampul of preservative-free sterile wate for injection as the diluent. Boxes of 12. NDC 0052-0442-10

**STORAGE:** PROTECT FROM LIGHT Store at 15°-30°C (59°-86°F)

**AFTER RECONSTITUTION:** Solution may be stored in refrigerator or kept at room temperature not to exceed 30° (86°F). DISCARD SOLUTION AFTER 24 HOURS. DISCARD UNUSED PORTION.

SINGLE USE VIALS—Manufactured for: ORGANON INC. By BEN VENUE LABORATORIES, INC., Bedford, Ohio 4414

**ORGANON PHARMACEUTICALS**, a Division of
Organon Inc., West Orange, N.J. 07052

# Anesthesia and Analgesia

## Journal of the International Anesthesia Research Society

3645 Warrensville Center Road, Cleveland, Ohio 44122 Telephones: (216) 295-1124 or 295-1130

## Editorial Board

### Editor in Chief

Nicholas M. Greene, MD, New Haven, Connecticut

### Editors

David R. Bevan, MA, MB, BChir, Montreal, Quebec, Canada
D. Ryan Cook, MD, Pittsburgh, Pennsylvania
Michael J. Cousins, MD, FFARACS, FFARCS, Adelaide, South Australia
Benjamin G. Covino, PhD, MD, Boston, Massachusetts
Norig Ellison, MD, Philadelphia, Pennsylvania
Mieczyslaw Finster, MD, New York, New York
Alison B. Froese, MD, Kingston, Ontario, Canada
Edward D. Miller JR, MD, Charlottesville, Virginia
Daniel M. Philbin, MD, Boston, Massachusetts
Cedric Prys-Roberts, MA, DM, PhD, Bristol, United Kingdom
J. Gerald Reves, MD, Durham, North Carolina
John H. Tinker, MD, Iowa City, Iowa
K.C. Wong, MD, PhD, Salt Lake City, Utah

### Book Review Editor

Norig Ellison, MD, Philadelphia, Pennsylvania

Editorial correspondence and manuscripts should be addressed to: NICHOLAS M. GREENE, MD, Editor in Chief, *Anesthesia and Analgesia*, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510 (Telephone: 203-785-4703). For information concerning preparation of manuscripts see "A Guide for Authors" published quarterly in the Journal. All articles published in this Journal become the property of the International Anesthesia Research Society. Reproduction in whole or part is not permitted except by written consent of the publisher and the author.

Books for review should be sent directly to the Book Review Editor, NORIG ELLISON, MD, Department of Anesthesia, University of Pennsylvania, Philadelphia, Pennsylvania 19104.

Reprints: For single copies, write directly to the senior author at the address listed on the title page. Quantity orders (minimum 100) processed through ELSEVIER SCIENCE PUBLISHING CO, INC, 52 Vanderbilt Avenue, New York, NY 10017, prices on request.

The International Anesthesia Research Society is a nonprofit, scientific, and educational corporation in the state of Ohio. Members of the Board of Trustees of the Society are: Douglas B. Craig, MD, Bruce F. Cullen, MD, E. Paul Didier, MD, Judith H. Donegan, MD, PhD, Noel W. Lawson, MD, John T. Martin, MD, Emerson A. Moffitt, MD, Dean H. Morrow, MD, Robert K. Stoelting, MD, and John L. Waller, MD. Emeritus Trustees are: Paul R. Dumke, MD, Kenneth K. Keown, MD, Morris T. Nicholson, MD, B.B. Sankey, MD, and T. H. Seldon, MD.

*Anesthesia and Analgesia* (ISSN 0003-2999) is issued monthly for the IARS in one indexed volume per year by Elsevier Science Publishing Co, Inc, 52 Vanderbilt Avenue, New York, NY 10017. Printed in USA. © 1985 International Anesthesia Research Society. Second class postage paid at New York, NY and at additional offices.

Subscription information for 1985 applying to IARS members: USA and possessions, $45.00 per year, in all other countries $55.00. Membership is available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine, or other disciplines who are engaged in active clinical practice of or research in anesthesiology. ASSOCIATE MEMBERSHIP is available to individuals certified, licensed, or accredited in anesthesia-related professions (CRNA, CRTT, RRT, Physician Assistant). EDUCATIONAL MEMBERSHIP (half the full member price) is available to interns, residents, students in nurse anesthesia and related training programs, for a 2- or 3-year period only upon completion of application including certification by applicant's program director.

All membership payments and correspondence regarding IARS member subscriptions should be sent to: Emerson A. Moffitt, MD, Executive Secretary, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, Ohio 44122.

Subscription information for 1985 applying to non-IARS members: Institutions, $90.00. Outside of the USA and possessions, please add $10.00 for surface postage and handling. For airmail, add $38.00 in USA, Canada, and Mexico, $22.00 for surface airlift to Europe, $34.00 for surface airlift to Japan, and $88.00 for airmail to the rest of the world. Postmaster: Send address changes to: *Anesthesia and Analgesia*, Elsevier Science Publishing Co, Inc, 52 Vanderbilt Avenue, New York, NY 10017.

Orders and inquiries regarding institutional and nonmember individual subscriptions should be directed to: Journals Fulfillment, Elsevier Science Publishing Co, Inc, 52 Vanderbilt Avenue, New York NY 10017. Subscriptions are entered for the calendar year, January–December.

Correspondence inquiries regarding IARS member subscriptions should be sent to the IARS at the Cleveland, Ohio address above. Correspondence regarding all other subscriptions should be sent to Elsevier.

Advertising inquiries should be addressed to: Pharmaceutical Media, Inc, 130 Madison Avenue, New York, NY 10016. The appearance of advertising in publications of the International Anesthesia Research Society does not constitute a guarantee or endorsement of the quality or value of such product or of the claims made for it by its manufactuer. Discussions, views, and recommendations as to medical procedures, choice of drugs, and drug dosages are the responsibility of the authors. Every effort has been made to ensure the accuracy of the information. The editor, publisher, or the Society, however, must disclaim any responsibility or liability. Readers are advised to check package insert information for each drug before administration.

See classified ads section for submission of classified material.

Single issues: Single copy information available from Elsevier Science Publishing Co, Inc, upon request. Back volume (all issues prior to 1983) information available from IARS.

Anesthesia
and Analgesia

# Contents

Volume 64, Number 10, October 1985

OBITUARY

Harold R. Griffith, MD, 1894–1985 — *David R. Bevan* — 945

SCIENTIFIC ARTICLES

Halothane and Isoflurane Do Not Decrease $PaO_2$ during One-Lung Ventilation in Intravenously Anesthetized Patients — *Stephen N. Rogers and Jonathan L. Benumof* — 946

Comparison of the Requirements for Hepatic Injury with Halothane and Enflurane in Rats — *Richard C. Lind, A. Jay Gandolfi, I. Glenn Sipes, and Burnell R. Brown* — 955

Antiarrhythmic Effect of Diltiazem During Halothane Anesthesia in Dogs and in Humans — *Naofumi Iwatsuki, Masato Katoh, Katsuhiko Ono, and Keisuke Amaha* — 964

Inhibition of Postoperative Pain by Continuous Low-Dose Intravenous Infusion of Lidocaine — *Jean Cassuto, Gunnar Wallin, Seth Högström, Anders Faxén, and Gunnar Rimbäck* — 971

Modulation of a GABA-Ergic Inhibitory Circuit in the In Vitro Hippocampus by Etomidate Isomers — *David Ashton and Albert Wauquier* — 975

Hospitalization for Miscarriage and Delivery Outcome among Swedish Nurses Working in Operating Rooms 1973–1978 — *H. Anders Ericson and A. J. Bengt Källén* — 981

Control and Accountability of Controlled Substance Administration in the Operating Room — *Ronald J. Moleski, Shirlene Easley, Paul G. Barash, Gil Primer, Nicte-ha Q. Shier, and Robert I. Schrier* — 989

Comparison of the Effects of General and Regional Anesthesia for Cesarean Section on Neonatal Neurologic and Adaptive Capacity Scores — *Therese K. Abboud, Shakuntala Nagappala, Kazushige Murakawa, Saul David, Sarkis Haroutunian, Makrouhi Zakarian, Thormason Yanagi, and Amir Sheikh-Ol-Eslam* — 996

Intracranial Pressure During Diltiazem-induced Hypotension in Anesthetized Dogs — *Paul Mazzoni, Joseph P. Giffin, James E. Cottrell, John Hartung, Christine Capuano, and Jeffrey M. Epstein* — 1001

Comparative Effects of Halothane, Enflurane, and Methoxyflurane on the Incidence of Abnormal Development Using Sea Urchin Gametes as an In Vitro Model System — *Robert E. Hinkley and Brent D. Wright* — 1005

CLINICAL REPORTS

Atracurium Pretreatment for Succinylcholine-induced Fasciculations and Postoperative Myalgia — *Laxmaiah Manchikanti, J. Blane Grow, Jerry A. Colliver, Michael G. Canella, and Clyde H. Hadley* — 1010

## CLINICAL REPORTS—*continued*

Inflation Device to Prevent Aortocaval Compression during Pregnancy — *Gerhard C. Endler and Rolf W. Donath* 1015

A Single-Unit Device for Differential Lung Ventilation with Only One Anesthesia Machine — *Takeyasu Yamamura, Hitoshi Furumido, and Yoshinori Saito* 1017

Verapamil Potentiation of Neuromuscular Blockade: Failure of Reversal with Neostigmine but Prompt Reversal with Edrophonium — *Ronald M. Jones, Jeremy N. Cashman, William R. Casson, and Michael P. Broadbent* 1021

Gastric Barotrauma: A Case Report and Theoretical Considerations — *Steven J. Barker and Thomas Karagianes* 1026

## LETTERS TO THE EDITOR

Subdural Migration of an Epidural Catheter — *Philip R. Bromage* 1029

Much Ado About Nothing: Trace Gaseous Metabolites in the Closed Circuit — *R. K. Baumgarten and W. J. Reynolds* 1029

Surgically Induced Hypertension in Brain Dead Patients — *Merlin D. Larson* 1030

Movement of the Distal End of the Endotracheal Tube during Flexion and Extension of the Neck — *Thomas J. K. Toung, Roger Grayson, James Saklad, and Henry Wang* 1030

A Simple Method for Improving the Safety of Percutaneous Cannulation of the Internal Jugular Vein — *Judith A. Fabian and Manoranjan C. Jesudian* 1032

Thoughts on Protamine Toxicity — *Stanley Brauer* 1033

Ketamine for Treatment of Priapism — *A. Villalonga, J. Beltran, C. Gomar, and M. A. Nalda* 1033

Myoclonus after Etomidate Anesthesia — *Jean Lumley and M. Morgan* 1034

Aminophylline Antagonism of the Residual Effects of Fentanyl Anesthesia — *Wang Ming-de and Ren Zhen-Lin* 1034

Common Sense in Statistical Analyses — *Denis L. Bourke* 1035

In Response — *Jerry A. Colliver and Laxmaiah Manchikanti* 1035

Optimization of Oxygenation by CPAP During One-Lung Anesthesia Using Nitrous Oxide:Oxygen — *Anis Baraka, Musa Muallem, Maurice Baroody, Robert Mansour, Abdel Nour Sibai, Sania Hroun, and Firyal Yamut* 1036

Precautions in Use of a New Endotracheal Tube for Laser Surgery — *Remigio Rubiano, Juei-Ling Chang, Christopher E. Larson, Robert A. Lawler, and Paul Rehkopf* 1037

Anesthesia-Related Transient Aphonia and Quadriplegia — *W. Davis Parker and Kay C. Parker* 1038

## BOOK REVIEWS

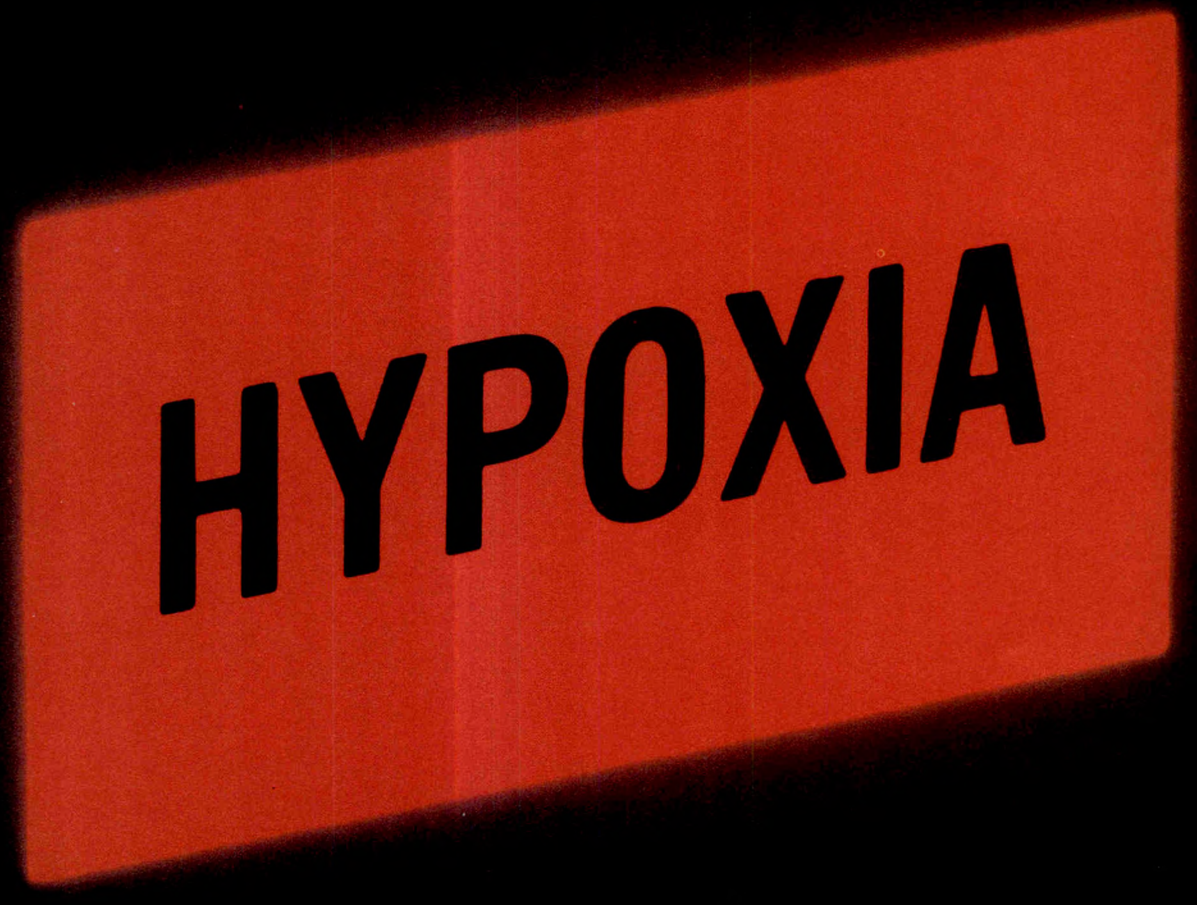
Endocrinology and the Anaesthetist. T. Oyama, ed. — *Arthur J. Klowden* 1039

Cardiovascular Anesthesia. Carol L. Lake — *William A. Lell and A. J. Wright* 1039

Erratum 1040

A Guide for Authors *after p.* 1040

# Detection will never be this simple…



# But today's continuous gas monitors can provide early warning of potentially catastrophic hypoxic episodes.

## Three means to an end.

Transcutaneous $O_2$. End tidal $CO_2$. $O_2$ saturation.

The continuous measurement of each is of proven usefulness in reducing the risks of anesthesia and improving the quality of intensive care.

Although the technologies may be recent, reliable monitoring systems are now available that make routine use both practical and affordable.

*"Transcutaneous $O_2$ and oxyhemoglobin saturation monitoring furnishes crucial information regarding oxygenation and oxygen delivery. These systems are easily applied, noninvasive, and reliable, and they yield information continuously. More importantly, they signal an early warning of critical incidents."* [1]

## Dispelling the misconceptions.

Do the readings from these noninvasive monitors correlate perfectly with arterial samples? No.

Does their use eliminate the need for drawing arterial blood gases? Again, no. However, their use may indicate when a blood gas sample is needed.

But these are not arguments against these important new sources of continuous information on patient oxygenation and ventilation.

Each technology has its own merits and, yes, its own limitations. Each requires an understanding of its capabilities for proper interpretation. And there is more being learned about the importance of these technologies every day.

*"Prevention of hypoxia is the most important goal of patient monitoring during anesthesia. Unfortunately, currently monitored variables of heart rate, blood pressure, breath sounds, and skin and blood color are not sensitive to the levels of oxygenation or to trends, but detect only the physiological consequences of inadequate oxygenation."* [2]

## The emergence of continuous gas monitoring.

You'll be hearing and reading a great deal about continuous gas monitoring in the months ahead.

Researchers are pinpointing undetected hypoxia as both a significant cause of anesthesia mishap and a factor in prolonged patient recovery.

Many prominent anesthesiologists are advising the use of continuous gas monitoring during an increasing number of procedures.

And several leading malpractice insurance firms are considering the recommendation of continuous gas monitoring as a means of countering the increase in anesthesia claims and premiums.

*"After an error has occurred, a period of time usually elapses before the error is discovered. Timing of the discovery is important, for prompt discovery may allow for correction of the error before any adverse consequences affect the patient."* [3]

## Novametrix' role.

Critical patient monitoring is Novametrix' only business. And we are convinced of both the viability and desirability of continuous gas monitoring and committed to its expanded use in the OR and ICU.

Novametrix has long been the acknowledged leader in the design and manufacture of transcutaneous $O_2/CO_2$ monitors, and offers a comprehensive line of equipment for both neonatal and adult use.

Recently, we've developed and marketed an innovative end tidal $CO_2$ monitoring system for the OR and ICU. And soon we plan to introduce a new pulse oximeter.

We feel it's time continuous gas monitoring reach its true potential through widespread adoption. Towards that end, we've assembled a collection of medical papers on continuous gas monitoring that we believe you'll find compelling.

For your own copy of these papers or information on Novametrix' full line of continuous gas monitors for the OR, call us toll-free at 1-800-243-3444.

Or write, Novametrix Medical Systems Inc., 1 Barnes Industrial Park Road, P.O. Box 690, Wallingford, CT 06492.

NOVAMETRIX

***See us at the ASA, Booths 1138-1141.***

---

1 Weingarten, M. M.D. *The Circular,* February/March 1984.

2 Barker, S. M.D., Ph.D. and Tremper, K. M.D., Ph.D. *Journal of Clinical Monitoring* Vol. 1, p. 130-134, April 1985.

3 Newbower, R. et al. *QRB/Quality Review Bulletin,* March 1981.

# INTERNATIONAL ANESTHESIA RESEARCH SOCIETY
# 60th CONGRESS—March 15–19, 1986—
# Caesars Palace Hotel, Las Vegas, Nevada

## PRELIMINARY MEETING INFORMATION

**Program/Registration Mailing:** The preliminary program, with daily schedule of presentations, will be sent out in mid-December to all IARS members. This will include registration card, hotel card, social activities and spouse program. (IARS members outside of North America who plan to attend the meeting can receive this material by airmail upon request.) Non-IARS members who wish to receive meeting/membership information should contact the Cleveland office.

| | |
|---|---|
| Schedule: | Registration: Saturday, March 15—1–5 PM (continues daily)<br>Scientific Program: Sunday, March 16, through Wednesday, March 19<br>Exhibits: Sunday, March 16, through Tuesday, March 18 |
| Program: | • T.H. Seldon Distinguished Lecture—Dr. J. Alfred Lee, Essex, England<br>• 26 Review Course Lectures<br>• Panels: Outpatient Anesthesia, Cardiovascular Anesthesia<br>• Over 100 Scientific Papers<br>• Scientific Poster Presentations<br>• Theme Luncheon Sessions<br>• Scientific Exhibits |
| Technical (Commercial) Exhibits: | Including a number of company sponsored Product Seminars |
| Spouse Program: | "Effective Tax Strategies" Seminar; area tours and other activities and presentations of interest. |
| Reduced Air Fare: | A special discounted fare will be available through United Airlines for IARS registrants. |
| CME Credit: | AMA/ACCME Category 1 (31 hr, est.) AANA credit to be confirmed. |

---

SCIENTIFIC EXHIBITS: Applications for scientific exhibit space are available from the IARS office. There is no absolute deadline for submission of applications. However, availability of space in the exhibit area will be a factor in considering applications received after January 1, 1986.

ARTS AND CRAFTS EXHIBIT: Responding to interest expressed by a number of members, the IARS will for the first time include an arts and crafts exhibit at the 1986 meeting. If you or your spouse would like to enter your personally done art or craft work, the rules and entry blanks are available from the Cleveland office. **The deadline for entry is January 31, 1986.**

International Anesthesia Research Society
3645 Warrensville Center Road, Cleveland, OH 44122
Tel: (216) 295-1124

( _______ ) Please send rules and entry blank for Arts and Crafts Exhibit.
( _______ ) Please send application for Scientific Exhibit space.

(Name) ________________________________
(Mail Address) ________________________________
________________________________

**Continuous $O_2$/$CO_2$ Monitoring Report #1**

**Subject:** Simple, low-cost pulse oximetry monitoring for timely hypoxemia detection.

# 1

# Pulse Oximetry
# NOVAMETRIX 500

Pulse oximetry is a noninvasive technique for assessing patient oxygenation.

An oximeter determines percentage hemoglobin saturation by measuring the absorbency of two different wavelengths of light passed through a pulsating arterial vascular bed. By comparing the ratios of the pulse amplitudes from each light, $SaO_2$ may be calculated under a wide range of hemodynamic conditions.

The use of pulse oximetry during routine anesthesia allows early recognition of hypoxemia permitting quick response to improve oxygenation.

Accurate and reliable, pulse oximetry represents a significant advance in anesthesia monitoring. In designing the Model 500 Pulse Oximeter, Novametrix retained the accuracy and reliability of earlier units, but added two vital elements: ease of use and low cost.

The microprocessor-controlled Novametrix 500 Pulse Oximeter needs no calibration or warm-up. Its digital electronic circuitry is entirely maintenance-free.

Setup is fast. Just push the power switch and the unit performs a quick self-diagnostic check. Then the 500's programmed menu quickly helps you set the high and low $SaO_2$ and pulse rate limits. Once the limits are set they are constantly visible. And the Novametrix 500 keeps them in memory indefinitely—for weeks or even months—until you decide to change them.

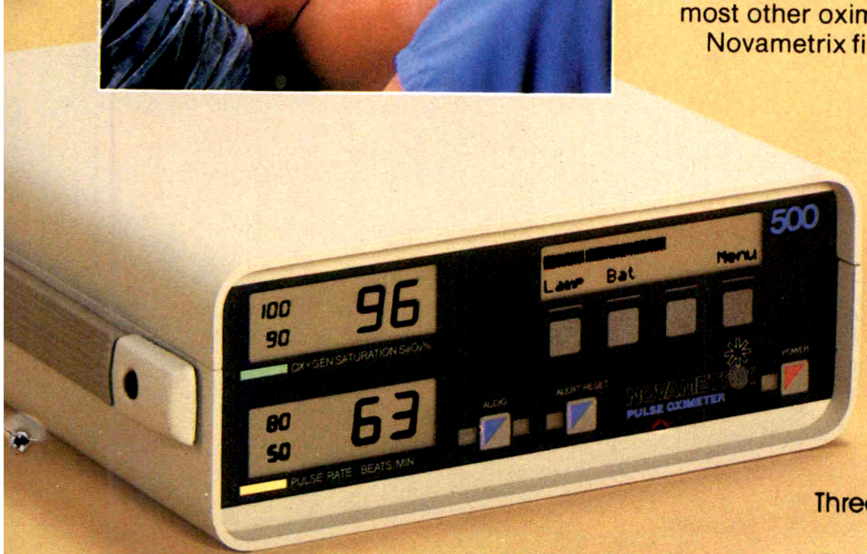
> ***"The Novametrix 500 is a simple, inexpensive means of monitoring oxygenation to reduce the incidence of anesthetic mishap during routine procedures."***

Operation is just as simple, with easy-to-read displays of $O_2$ saturation and pulse rate. A message center displays a bar graph of pulse amplitude as well as providing specific information regarding any alert condition. In addition, there's an audible pulse signal that changes in tone—up or down to reflect changes in $SaO_2$—so you can keep your eyes on the patient.

The Novametrix 500 Pulse Oximeter is small, lightweight (under 10 lbs.), and operates for a full 20 hours on a single battery recharge. (Not just an hour or two of battery backup power like most other oximeters.)

Novametrix finger, ear, and versatile flexible sensors are small, ruggedly built, and designed for easy application to patients of all ages. And Novametrix' unique selectable response time eliminates false alerts due to motion artifact.

For full technical details—and the surprisingly low price—write Novametrix Medical Systems Inc., 1 Barnes Industrial Park Road, P.O.Box 690, Wallingford, CT 06492. Or call us toll-free at 1-800-243-3444.



Model 500 Pulse Oximeter.

Pulse Oximetry.
End Tidal $CO_2$.
Transcutaneous $O_2$/$CO_2$.
Three technologies...one source.

**NOVAMETRIX**

***See us at the ASA, Booths 1138-1141.***

# Soothing news for busy anesthesiologists

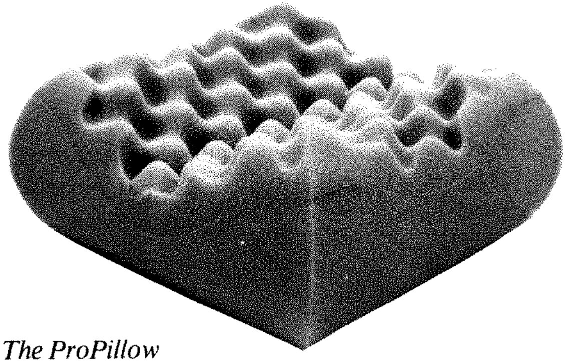
Dr. Smith was having another busy day in surgery. One Swan-Ganz placement had been unusually time-consuming. Plus the patient had been difficult to intubate. To top it off, the pump time had been excessive.

Down the hall, Dr. Jones had a marathon case involving a young woman undergoing a tuboplasty for infertility. Finally, 5½ hours later the surgeons were closing the skin. He heaved a sigh of relief and automatically leveled the table from the previous several hours where the Trendelenberg position had been necessary.

But these two stories don't end here. About 28 days later, *both patients had a bald spot about the size of a silver dollar at the occiput. . . exactly where their heads were resting on the table for hours on end.* They were each advised by their surgeons that they had a 50% chance of their hair growing back within the next year. But there was an equal chance that their hair wouldn't grow back at all. The anesthesiologists on both cases were never told of the problem.

## The ProPillow takes the pressure off

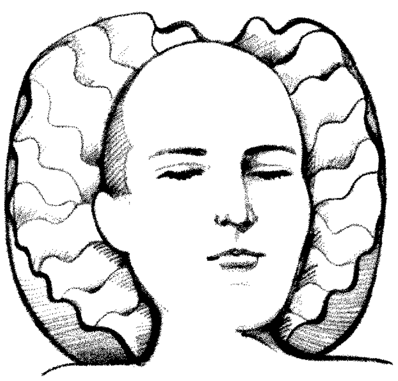
The ProPillow Anesthesia Pillow helps "take off the pressure" to the circulation of the face and scalp during prolonged anesthesia. It's unique "hills and valleys" construction creates a protective effect by evenly distributing the weight of the head and neck. Result: no more pressure in one area greater than any other area. And those precipitous swings in blood pressure are less likely to result in ischemia to the scalp. All this lessens the chance of post-op alopecia.



*The ProPillow Anesthesia Pillow*

## The end of the juggling act

The ProPillow lets you off gracefully from attempts to juggle the heavy head (10 lbs.) during intubation. The ProPillow Anesthesia Pillow stabilizes (by gently gripping) the patient's head in the neutral, "sniffing", position. It even helps free up one of your hands when you're using a mask for short cases.



*The ProPillow Anesthesia Pillow stabilizes the head, supports the neck and helps take the pressure off.*

## An eye for details

Awake patients really appreciate the comfort of the ProPillow Anesthesia Pillow. Especially the eye patients who are undergoing removal of cataracts with intra-ocular lens implants. And the ProPillow fits inside the frame used by Opthalmologists during this tedious microsurgery. Less squirming. . . and possibly sedation required.

## And the price is right

Because of the ProPillow's reasonable price, some say we should call it disposable. But it is made to last for up to 50 cases. You can use a nurse's bouffant cap to cover the ProPillow. Or even spot wash and air-dry it. It's made from a bright blue, breathable, resilient polyurethane foam that's 100% non-allergenic and non-irritating to skin.

It's easy to order the ProPillow Anesthesia Pillow! Call us **TOLL FREE** at **(800) 227-0517 outside California**, or **(800) 554-5541 inside California.** Or, give this page to your head nurse or purchasing agent to get the ProPillow promptly. We ship within 24 hours. *Pediatric Size available, ask for details.

**ProTechPacific**
**1221 Andersen Drive**
**San Rafael, CA 94901**

Makers of the **ProPillow Anesthesia Pillow, NECK-PIL-O Neck Support Pillow, DIXSEY Hip Abduction pillow** and the new **STRAPEZE * Velcro Endotracheal Tube stabilizer.**

**Continuous $O_2/CO_2$ Monitoring Report #2**

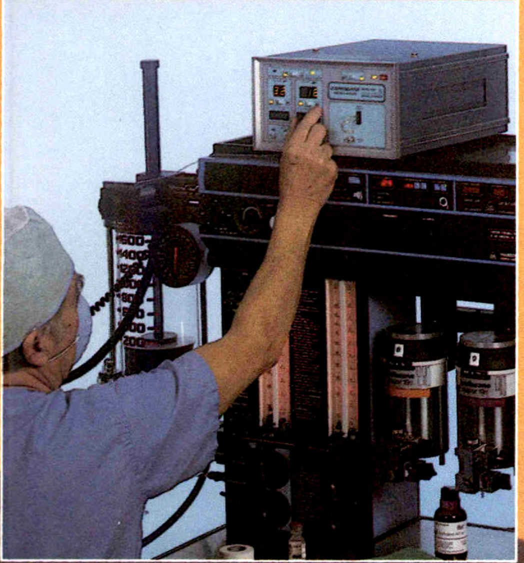
**Subject:** Cost-effective capnography for the OR; calibration and condensation problems solved.

# 2

# End Tidal $CO_2$
# NOVAMETRIX 1250

The measurement of end tidal carbon dioxide by a modern on-line analyzer provides a close approximation of alveolar partial pressure of $CO_2$.

Continuous measurement of $ETCO_2$ in the OR allows up-to-the-minute assessment of the adequacy of ventilation, and assists in the timely diagnosis of intraoperative problems or metabolic trends allowing early intervention to prevent adverse outcome.



Capnography in the OR used to mean long warm-up periods, tedious calibration sessions, and a constant struggle to keep the sampling circuit clear of moisture.

Thanks to microelectronic technology, this is no longer the case. And none of the newer $ETCO_2$ monitors use this technology better than the Novametrix 1250.

But while the electronics of the Capnogard™ 1250 are complex, they actually make the monitor simpler to use. Push the system power switch and the unit is up and monitoring in less than two minutes. And its innovative microprocessor control system keeps it that way, ensuring continuous reliable operation.

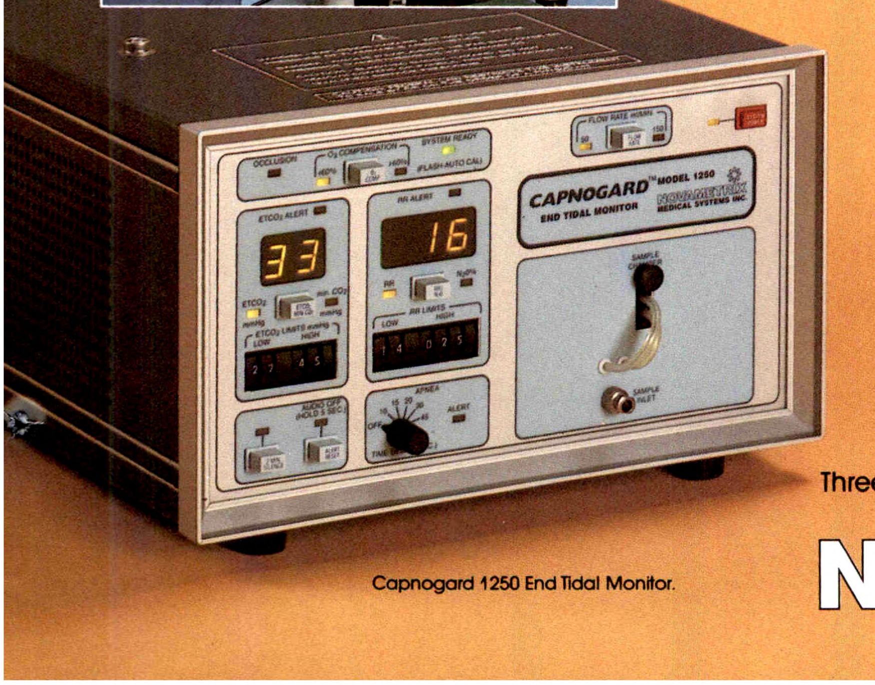
> ***"An end tidal monitor you don't need to calibrate? Yes. The Capnogard 1250 from Novametrix."***

The designers of the Capnogard noted how moisture problems overwhelmed the water traps of even the best end tidal monitors. So they developed a dehumidification interface kit with a semipermeable tube drying system and a built-in disposable particulate filter. Then they incorporated a front panel accessible sample chamber that could be manually cleared in under a minute right in the OR. Moisture a problem with your end tidal monitoring? Not if you're using the Capnogard 1250.

And, thanks to the 1250's unique auto-zeroing system, you can forget about time-consuming daily calibration sessions. (Semiannual reverification of calibration is recommended.)

Unlike many $CO_2$ analyzers, the 1250 was designed with the OR in mind. So you'll find features like direct measurement of $N_2O$; automatic and continuous $N_2O$ compensation; large LED readouts; apnea alert; two-minute silence, audio off, and alert reset buttons; sample exhaust for gas scavenging; and analog outputs for recorder and scope displays.

For details on the Capnogard 1250—and its surprisingly low price—write Novametrix Medical Systems Inc., 1 Barnes Industrial Park Road, P.O. Box 690, Wallingford, CT 06492. Or call us toll-free at 1-800-243-3444.



Capnogard 1250 End Tidal Monitor.

Pulse Oximetry.
End Tidal $CO_2$.
Transcutaneous $O_2/CO_2$.
Three technologies...one source.

**NOVAMETRIX**

***See us at the ASA, Booths 1138-1141.***

## CORRECTION NOTICE:

A typographical error appears in the following publication. . .

Atlee: **Perioperative Cardiac Dysrhythmias: Mechanisms, Recognition, Management**
ISBN 0-8151-0345-X

The error in this publication is on page 404, table 9-2-DRUGS USED TO TREAT CARDIAC DYSRHYTHMIAS, DOSES (IV), AND PRINCIPAL INDICATIONS. The dosage for the drug BRETYLIUM is incorrectly stated. The dosage column should read:

B = 5—10mg/kg (up to 30 mg/kg daily);
I‡ = 1—2mg/min or 5—10 mg/kg over 6—8 hr

*An errata slip making this correction is available. Purchasers who wish a copy, may contact Year Book Medical Publishers at the address or telephone number below.*

**YEAR BOOK MEDICAL PUBLISHERS**
**35 EAST WACKER DRIVE**
**CHICAGO, ILLINOIS 60601**
**1-800-621-9262**

---

## HAROLD R. GRIFFITH CHAIR IN ANESTHESIA

A fund has been established to endow a chair to honour the memory of the renowned Canadian physician, anesthetist, and scientist whose association with McGill University extended over forty years.

This chair will be dedicated to the further development within the McGill department of scientific investigation and the promotion of education in research.

Individuals wishing to contribute are asked to forward cheques, made payable to McGill University (Harold R. Griffith Fund).

*Address:*

**University Secretariat**
**McGill University**
**F. Cyril James Building**
**Room 608**
**845 Sherbrooke West**
**Montreal, Quebec**
**H3A 2T5**

---

**See Nitrous Oxide $N_2O$ and Other Publications at Booth 837**

NITROUS OXIDE/$N_2O$

Editor: **Edmond I. Eger II, M.D.,**
Professor and Vice Chairman for Research,
Department of Anesthesia,
University of California, San Francisco

After 140 years of use, nitrous oxide is now known to be more than an inert vehicle for other, more potent anesthetics. Nitrous oxide affects the function of every body tissue significantly. Optimum application requires a full appreciation of both the benefits and potential hazards of this anesthetic substance.

***Nitrous Oxide/$N_2O$*** is a complete resource on the subject. It describes what is known about nitrous oxide – applications and contraindications – and debates its continued clinical use. The current clinical applications of $N_2O$ are reviewed by means of:

- thorough discussion of $N_2O$ pharmacology and distribution
- detailed summary of known side effects and toxicity
- practical guidelines for avoiding and managing these effects

Finally, the case for administering this anesthetic is carefully and candidly assessed in chapters by proponents of both views. ***Nitrous Oxide/$N_2O$*** is a controversial work that everyone using the drug will want to read.

**Contents.** Preface. Contributors. A History of Nitrous Oxide. Physics, Chemistry, and Manufacture of Nitrous Oxide. Nitrous Oxide Analgesia. MAC. Nitrous Oxide Delivery Systems. Pharmacokinetics. Respiratory Effects of Nitrous Oxide. Cardiovascular Effects of Nitrous Oxide. Central Nervous System Effects of Nitrous Oxide. Neuromuscular Effects of Nitrous Oxide. Nitrous Oxide in Obstetrics. Metabolism of Nitrous Oxide. Nitrous Oxide Inactivates Methionine Synthetase. Mutagenicity, Carcinogenicity, and Teratogenicity of Nitrous Oxide. Nitrous Oxide Abuse. Toxicity of Nitrous Oxide. The Use of Nitrous Oxide by Dentists. Nitrous Oxide in Veterinary Practice and Animal Research. Controlling Occupational Exposure to Nitrous Oxide. Should We Not Use Nitrous Oxide. We Should Continue to Use Nitrous Oxide. Epilogue. Index.

1984 416 pages 0-444-00860-8 cloth $37.50
(Distributed outside the U.S.A. and Canada by Edward Arnold Ltd., London.)

Order from your usual supplier or
Elsevier Science Publishing Co., Inc.
P.O. Box 1663, Grand Central Station, New York, NY 10163

**Note:** Price subject to change without notice.
In NY State please add applicable sales tax. 8/85 EB343

ELSEVIER

**Continuous $O_2/CO_2$ Monitoring Report #3**

**Subject:** Compact, easy-to-use $P_{tc}O_2$ monitoring for OR patients.

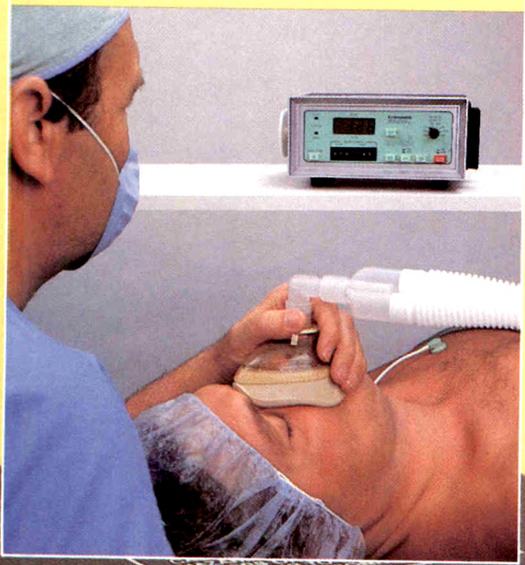
# 3

# Transcutaneous $O_2$
# NOVAMETRIX 811

"$P_{tc}O_2$ is a useful variable because it is a noninvasive 'global' monitor of patient oxygenation. It can give an early warning of decreasing oxygen delivery, thus allowing the treatment of impending hypoxia before it occurs." [1]

"$P_{tc}O_2$ monitoring proved also to act as an early warning device for impending hypoxemia and hemodynamic compromise, thereby facilitating very early therapeutic intervention." [2]

1 Barker, S. M.D., Ph.D. and Tremper, K. M.D., Ph.D. *Journal of Clinical Monitoring, 1:* 130-134 (1985).
2 Chubra-Smith, N.M. M.D., et. al. *Anesthesia/Analgesia 64:* 185-304 (1985).



Along with a growing recognition of the usefulness of continuous gas monitoring during surgery came the need for a cost-effective $P_{tc}O_2$ monitor suitable for routine use on patients in the OR. The Novametrix 811 monitor meets that need.

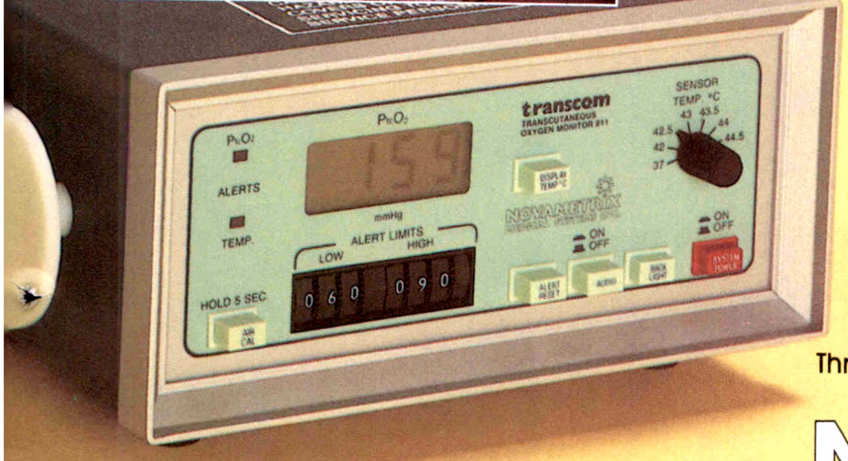
> ***"The Novametrix 811 is the first transcutaneous monitor to deal with the special requirements of all OR patients."***

Simplicity is a key feature of the Novametrix 811. Activate the system power switch, push the automatic air calibration button, and you're ready to monitor.

And Novametrix knows that space is scarce in a crowded OR, so the 811 is compact and can be equipped for pole mounting. The 811 is also a true portable transcutaneous monitor, and may be operated on AC power or on its rechargeable gel cell for up to eight hours between recharges.

An eight-position temperature selection switch offers a choice of sensor temperatures for operation. Visual display of both actual and selected temperature provides reassurance of proper sensor operation. And while we're talking about sensors, remember that Novametrix sensors are recognized for their rugged construction and durability, so you can count on their withstanding the occasional rough handling they'll receive in the OR.

For complete information on the Novametrix Model 811 Transcutaneous $O_2$ monitor, along with details on its surprisingly low price, call us toll-free at 1-800-243-3444. Or write Novametrix Medical Systems Inc., 1 Barnes Industrial Park Road, P.O. Box 690, Wallingford, CT 06492.



Model 811 Transcutaneous $O_2$ Monitor.

Pulse Oximetry.
End Tidal $CO_2$.
Transcutaneous $O_2/CO_2$.
Three technologies...one source.

**NOVAMETRIX**

***See us at the ASA, Booths 1138-1141.***

# Anaquest

## introduces

# Enlon™

(edrophonium chloride injection, USP)

**For faster reversal of neuromuscular blockade with fewer side effects**

**From the developers of**
**Ethrane®** (enflurane) **and Forane®** (isoflurane)

Anaquest
2005 West Beltline Highway
Madison WI 53713 2318
608 273 0019 800 ANA DRUG
A Division of BOC Inc

**BOC Health Care**

© 1985 BOC Inc

# 60-second reversal of neuromuscular blockade

- **Onset of reversal significantly faster than with neostigmine or pyridostigmine**—60 seconds versus 7 minutes for neostigmine, 12 minutes for pyridostigmine.[1,2]
- **Duration of reversal comparable to that of neostigmine**—66 minutes versus 76 minutes for neostigmine.[1,2*]
- **Significantly fewer muscarinic side effects and lower atropine requirement than with neostigmine**—edrophonium, 0.5 mg/kg, with only 7 μg/kg atropine, produced minimal change in heart rate or mean arterial pressure compared to noticeable changes in both indexes following neostigmine, 0.04 mg/kg, using *twice* the atropine dose (15 μg/kg).[1,2]
- **May be the reversal agent of choice for atracurium and vecuronium** "...compared with neostigmine, edrophonium has a more complete spectrum of atracurium reversal characteristics, and...antagonizes more rapidly residual atracurium-induced neuromuscular blockade."[3]

  "Edrophonium may in fact be the preferred reversal agent for routine use with [vecuronium], having the advantages that restoration of voluntary muscle function is very rapid, and that the relatively small dose of atropine required minimizes the unwanted side-effects of this drug."[4]

***Note:** When duration of action is adjusted for differences in onset of action, the relative durations are 65 minutes for edrophonium and 69 minutes for neostigmine.

1. Cronnelly R, Morris RB, Miller RD: Edrophonium: duration of action and atropine requirement in humans during halothane anesthesia. Anesthesiology 57:261-266, 1982. 2. Miller RD, et al: Comparative times to peak effect and duration of action of neostigmine and pyridostigmine. Anesthesiology 41:27-33, 1974. 3. Jones RM, Pearce AC, Williams JP: Recovery characteristics following antagonism of atracurium with neostigmine or edrophonium. Br J Anaesth 56:453-457, 1984. 4. Baird WLM, Bowman WC, Kerr WJ: Some actions of ORG NC45 and of edrophonium in the anaesthetized cat and in man. Br J Anaesth 54:375-385, 1982.

Please see use information on next page.

# Anaquest

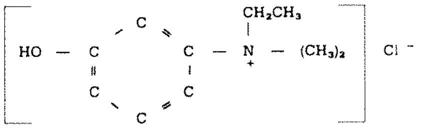
# introduces

# Enlon™ (edrophonium chloride injection, USP)

# 60-second reversal of neuromuscular blockade

## DESCRIPTION

ENLON (edrophonium chloride injection, USP) is a rapid acting cholinergic (cholinesterase inhibitor). Chemically edrophonium chloride is ethyl (m-hydroxyphenyl) dimethylammonium chloride and its structural formula is:



ENLON contains in each mL of sterile solution:

(vial) 10 mg edrophonium chloride compounded with 0.45% phenol and 0.2% sodium sulfite as preservative, buffered with sodium citrate and citric acid. Its pH is adjusted to approximately 5.4

## CLINICAL PHARMACOLOGY

ENLON (edrophonium chloride injection, USP) activates neuromuscular transmission primarily by inhibiting or inactivating acetylcholinesterase. By inactivating the acetylcholinesterase enzyme, acetylcholine is not hydrolyzed by acetylcholinesterase and is thereby allowed to accumulate. The accumulation of acetylcholine at the sites of cholinergic transmission facilitates transmission of impulses across the myoneural junction.

## INDICATIONS AND USAGE

ENLON (edrophonium chloride injection, USP) is recommended as a reversal agent or antagonist of nondepolarizing muscle relaxants such as tubocurarine, metocurine, atracurium, vecuronium, or pancuronium. It is not effective against depolarizing relaxants such as succinylcholine and decamethonium. It is also useful if used adjunctively in the treatment of respiratory depression caused by curare overdosage. ENLON is recommended for use in the differential diagnosis of myasthenia gravis. It may also be used as an adjunct to evaluate treatment requirements of the disease, and for evaluating emergency treatment in myasthenic crisis. It is not recommended for maintenance therapy in myasthenia gravis.

## CONTRAINDICATIONS

ENLON (edrophonium chloride injection, USP) is not to be used in patients with known hypersensitivity to anticholinesterase agents, or in patients having urinary obstructions of mechanical type.

## WARNINGS

It is recommended that 1 mg atropine sulfate should be made available for immediate use, to counteract any severe cholinergic reaction. ENLON (edrophonium chloride injection, USP) should be used with caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Isolated instances of cardiac and respiratory arrest following administration of edrophonium chloride have been reported. It is postulated that these are vagotonic effects.

## PRECAUTIONS

**General:** As with any antagonist of nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance. Should a patient develop "anticholinesterase insensitivity" for brief or prolonged periods, the patient should be carefully monitored and the dosage of anticholinesterase drugs reduced or withheld until the patient again becomes sensitive to them.

**Drug Interactions:** The drug should not be administered prior to the administration of any nondepolarizing muscle relaxants. The drug should be administered with caution to patients with symptoms of myasthenic weakness who are also on anticholinesterase drugs. Anticholinesterase overdosage (cholinergic crisis) symptoms may mimic underdosage (myasthenic weakness) so the use of this drug may worsen the condition of these patients (see OVERDOSAGE section for treatment).

**Pregnancy Category C:** It is not known whether ENLON (edrophonium chloride injection, USP) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity, since there have been no adequate and well controlled studies in humans.

**Labor and Delivery:** The effect of ENLON on the mother and fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary is not known. The effect of the drug on the later growth, development and functional maturation of the child is also unknown.

**Nursing Mothers:** The safety of ENLON during lactation in humans has not been established.

## ADVERSE REACTIONS

A patient in myasthenic crisis, being treated with ENLON (edrophonium chloride injection, USP) should be observed for bradycardia or cardiac standstill and cholinergic reactions if an overdosage is given. Reactions common to anticholinesterase agents such as edrophonium chloride are:

**Cardiovascular:** arrhythmias (especially bradycardia), fall in output leading to hypotension;

**Respiratory:** increased tracheobronchial secretions, laryngospasm, bronchiolar constriction and respiratory muscle paralysis;

**Neurologic:** convulsions, dysarthria, dysphonia, and dysphagia;

**Gastrointestinal:** nausea, vomiting, increased peristalsis, increased gastric and intestinal secretions, diarrhea, abdominal cramps;

**Musculoskeletal:** weakness and fasciculations;

**Miscellaneous:** increased urinary frequency, diaphoresis, increased lacrimation, pupillary constriction, diplopia, and conjunctival hyperemia.

## OVERDOSAGE

Muscarine-like symptoms (nausea, vomiting, diarrhea, sweating, increased bronchial and salivary secretions and bradycardia) may appear with overdosage (cholinergic crisis) of ENLON (edrophonium chloride injection, USP) but may be managed by the use of atropine. Obstruction of the airway by bronchial secretions can arise and may be managed with suction (especially if tracheostomy has been performed) and by the use of atropine. Signs of atropine overdosage such as dry mouth, flush and tachycardia should be avoided as tenacious secretions and bronchial plugs may form. Should edrophonium chloride overdosage occur:

1. Maintain respiratory exchange.
2. Monitor cardiac function.

Appropriate measures should be taken if convulsions or shock are present.

## DOSAGE AND ADMINISTRATION

**The recommended adult intravenous injection for antagonism of neuromuscular block:**

Administer 1 mL (10 mg) slowly within a period of 30 to 45 seconds, the dosage may be repeated to a maximum total dose of 4 mL (40 mg). Its onset of action is manifest within 30 to 60 seconds after injection. Response should be monitored carefully and assisted ventilation should always be employed. When given to counteract muscle relaxant overdosage, the dose effect on respiration should be observed prior to repeat dosages and assisted ventilation should be employed.

**ENLON (edrophonium chloride injection, USP) Test in Differential Diagnosis of Myasthenia Gravis:**

**Adults:**

**Intravenous Dosage:** Prepare a tuberculin syringe with 1 mL (10 mg) of ENLON and an intravenous needle; intravenously inject 0.2 mL (2 mg) within 15 to 30 seconds. The needle should be left in situ. If a cholinergic reaction (muscarinic side effects, skeletal muscle fasciculations and increased muscle weakness) occurs, discontinue test and intravenously administer 0.4 mg to 0.5 mg atropine sulfate. Inject the remaining 0.8 mL (8 mg) only if no reaction occurs after 45 seconds. The test may be repeated after one-half hour.

**Intramuscular Dosage:** Intramuscularly inject 1 mL (10 mg) of ENLON. If hyperreactivity (cholinergic reaction) is demonstrated, retest the patient after one-half hour with another intramuscular injection of 0.2 mL (2 mg) ENLON. This will eliminate the possibility of false-negative reactions.

**Children:**

**Intravenous dose in children weighing up to 75 pounds:**

Intravenously inject 0.1 mL (1 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 0.5 mL (5 mg). The recommended dose in infants is 0.05 mL (0.5 mg).

**Intravenous dose in children weighing above 75 pounds:**

Intravenously inject 0.2 mL (2 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 1 mL (10 mg).

**Intramuscular Dose:** Intramuscularly inject 0.2 mL (2 mg) ENLON in children weighing up to 75 pounds; above this weight, the dose is 0.5 mL (5 mg). All signs of hyperreactivity (cholinergic reaction) noted in the intravenous test will be demonstrated in the intramuscular test; however, there is a two to ten minute delay before reaction.

**ENLON (edrophonium chloride injection, USP) Test to Evaluate Treatment Requirements in Myasthenia Gravis:**

The test dose of ENLON should follow one hour after oral intake of the drug being used to treat the disease. The recommended dose is 0.1 mL to 0.2 mL (1 mg to 2 mg) administered intravenously. Response to ENLON test dose in treated myasthenic patients is summarized as follows:

**Undertreated patient:** Myasthenic response; characterized by increased muscle strength (ptosis, diplopia, dysphonia, dysphagia, dysarthria, respiration, limb strength). This indicates inadequate treatment of the myasthenic condition.

**Controlled patient:** Adequate response; characterized by no change in muscle strength with minimal side reactions (lacrimation, diaphoresis, salivation, abdominal cramps, nausea, vomiting, diarrhea). Fasciculations (orbicularis oculi, facial muscles, limb muscles) may or may not occur. The response indicates that therapy is stabilized.

**Overtreated patient:** Cholinergic response; characterized by decreased muscle strength and severe side reactions. Fasciculations may be observed. This response occurs in myasthenics who have been overtreated with anticholinesterase drugs.

**ENLON (edrophonium chloride injection, USP) Test in Crisis:**

Crisis in the myasthenic patient is characterized as a state of severe respiratory distress with inadequate ventilatory exchange, and unpredictable response to medication. If the patient is apneic, achieve ventilatory exchange immediately to avoid cardiac arrest and irreversible central nervous system damage.

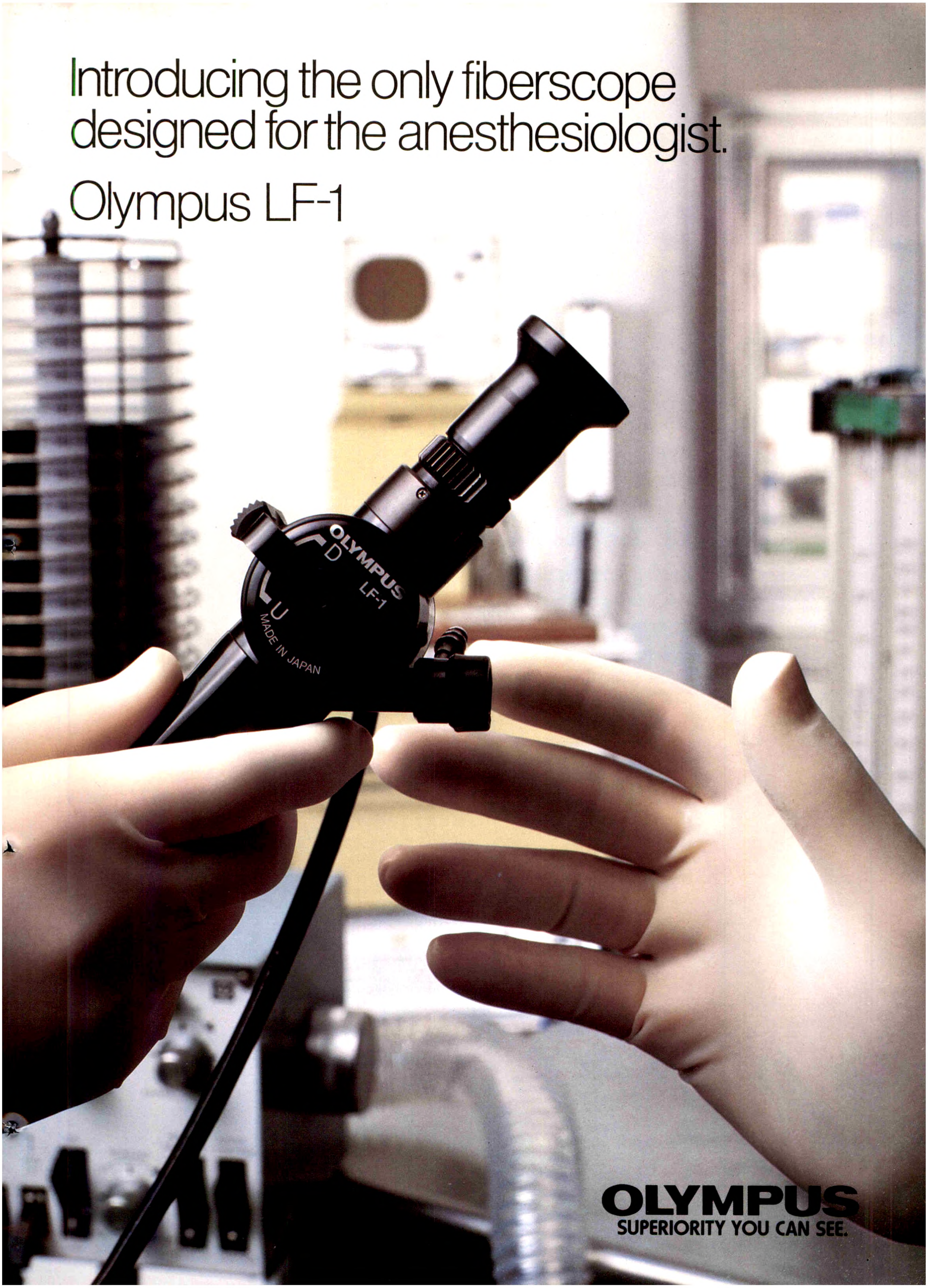
The ENLON Test should not be conducted until respiratory exchange is maintained. The cholinergic patient will exhibit further weakness in the muscles of respiration and will have increased oropharyngeal secretions if ENLON is administered. Whereas, upon administration of ENLON the myasthenic patient will demonstrate improved respiration and can be given additional medication. To perform the test prepare a syringe with 0.2 mL (2 mg) ENLON and intravenously inject 0.1 mL (1 mg). The patient's cardiac and respiratory actions should be observed for change. The remaining 0.1 mL (1 mg) may be injected after one minute if no response is noted. If, after the entire 0.2 mL (2 mg) dose has been injected, no improvement in respiration occurs, discontinue all anticholinesterase drugs. Controlled ventilation can be achieved by tracheostomy with assisted respiration.

## HOW SUPPLIED

ENLON (edrophonium chloride injection, USP):

**NDC** 10019-873-15 15 mL multidose vials.

2-85



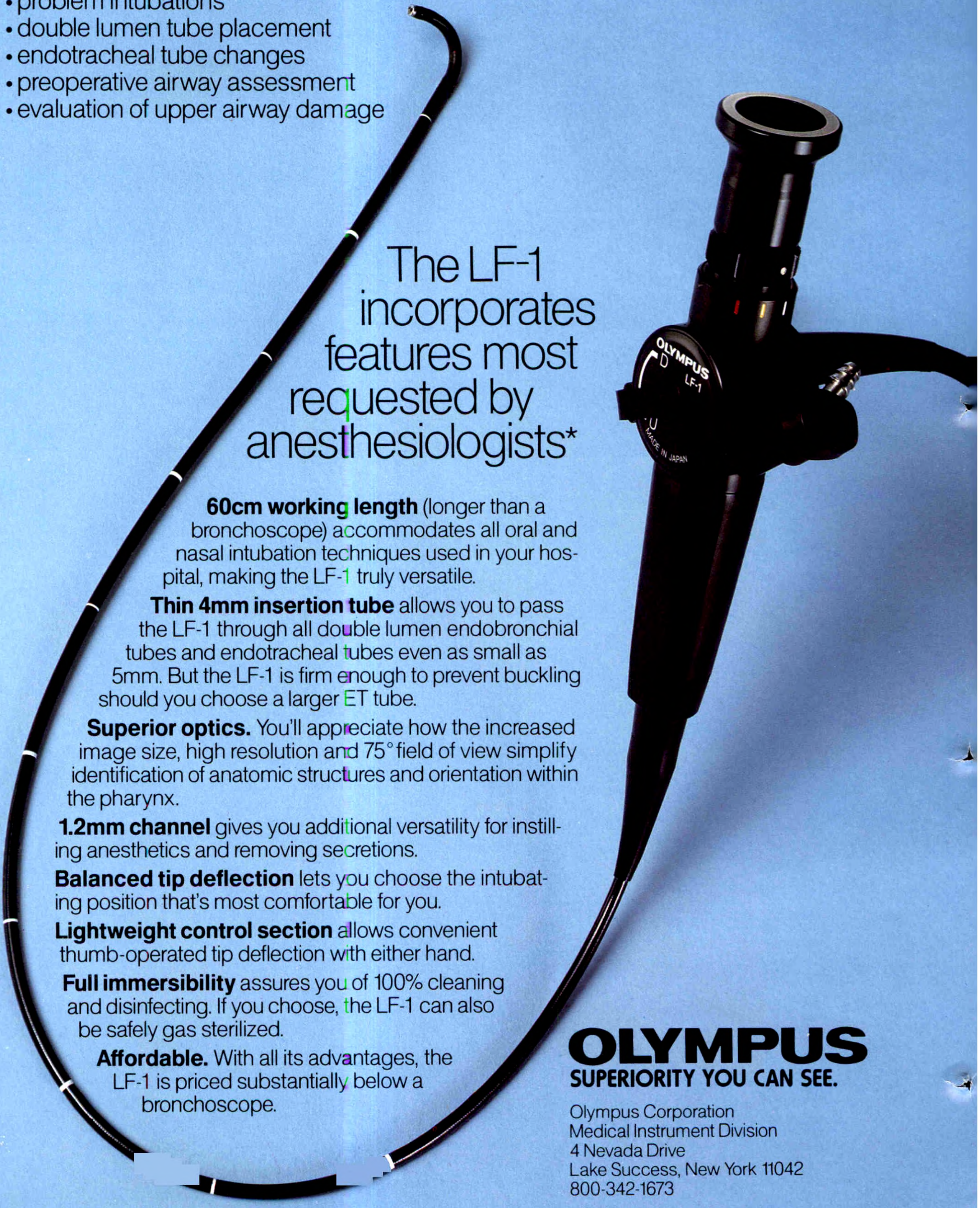
Introducing the only fiberscope designed for the anesthesiologist.

Olympus LF-1

**OLYMPUS**
SUPERIORITY YOU CAN SEE.

# The Olympus LF-1 Intubation Scope designed specifically for:

- problem intubations
- double lumen tube placement
- endotracheal tube changes
- preoperative airway assessment
- evaluation of upper airway damage



## The LF-1 incorporates features most requested by anesthesiologists*

**60cm working length** (longer than a bronchoscope) accommodates all oral and nasal intubation techniques used in your hospital, making the LF-1 truly versatile.

**Thin 4mm insertion tube** allows you to pass the LF-1 through all double lumen endobronchial tubes and endotracheal tubes even as small as 5mm. But the LF-1 is firm enough to prevent buckling should you choose a larger ET tube.

**Superior optics.** You'll appreciate how the increased image size, high resolution and 75° field of view simplify identification of anatomic structures and orientation within the pharynx.

**1.2mm channel** gives you additional versatility for instilling anesthetics and removing secretions.

**Balanced tip deflection** lets you choose the intubating position that's most comfortable for you.

**Lightweight control section** allows convenient thumb-operated tip deflection with either hand.

**Full immersibility** assures you of 100% cleaning and disinfecting. If you choose, the LF-1 can also be safely gas sterilized.

**Affordable.** With all its advantages, the LF-1 is priced substantially below a bronchoscope.

**OLYMPUS**
**SUPERIORITY YOU CAN SEE.**

Olympus Corporation
Medical Instrument Division
4 Nevada Drive
Lake Success, New York 11042
800-342-1673

---

*From a market survey conducted by Olympus Corporation in January, 1983.

©1985 Olympus Corporation

# IARS MEMBERSHIP

## FOR YOUR IN-TRAINING AND CONTINUING MEDICAL EDUCATION

The International Anesthesia Research Society is a non-profit, scientific and educational corporation of the State of Ohio, founded in 1922 "to foster progress and research in anesthesia." To this end the Society

Publishes the oldest journal in the specialty, *Anesthesia and Analgesia*

Sponsors an annual scientific meeting (Congress) which is held in March each year

Funds anesthesia-related research through the IARS B.B. Sankey Anesthesia Advancement Award

Membership in the IARS is voluntary; it is also separate and distinct from membership in any other local, state, regional or national anesthesia organization or association. Membership is open to individuals who qualify in the various categories shown below; who complete the appropriate application and submit it to the IARS Cleveland office with the applicable dues. All memberships include a subscription to *Anesthesia and Analgesia*. Members and Associate Members are entitled to a reduced registration fee at the IARS annual meeting; Educational Members pay no registration fee.

## . . . . MEMBERSHIP CATEGORIES . . . .

**MEMBERSHIP:** Open to individuals with doctorate degrees, who are licensed to practice in the medical, osteopathic, dental or veterinary medicine fields (i.e., MD, MB, DO, DDS, DMD, DVM); and to individuals with doctorate degrees in any scientific discipline (PhD), who are engaged in academic, private or commercial research.

**ASSOCIATE MEMBERSHIP:** Open to individuals in the allied health professions, duly certified by their professional accrediting organization as nurse anesthetists (CRNA); respiratory therapists or technicians (RRT or CRTT); physician/anesthesia assistants (PA/MMS); and other allied health professionals in anesthesia-related practice.

*Annual Dues for Members and Associate Members:* $45.00 U.S.; $55.00 foreign. These memberships are entered on a calendar year basis only.

**EDUCATIONAL MEMBERSHIP:** Open (with certification by program director) to doctors (interns/residents) enrolled in anesthesiology training programs; nurses enrolled in nurse anesthesia schools; students enrolled in programs leading to certification as physician assistants, respiratory therapists or technicians

*Annual Dues for Educational Members:* One-half of member rate. These memberships are entered in January or July for 2, 3, or 4 year periods. Applications, certified by program directors, must accompany check to cover full membership period.

---

International Anesthesia Research Society
3645 Warrensville Center Road, Cleveland, Ohio 44122, USA

Please send me ______ application(s) for: Membership (______)
Associate Membership (______)
Educational Membership (______)

Please print clearly: ________________________________
Name and Degree (MD, DO, CRNA, RN, RRT, etc.)

________________________________
Street Address City, State, Zip Code (country)

**Introducing STRAPEZE™**

While others slip and slide all over the place, we've made a name for ourselves by staying put.

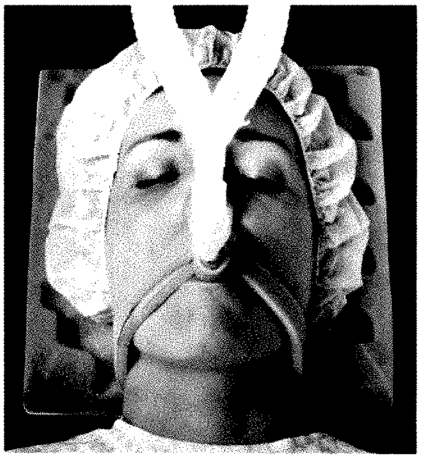
**No more fumbling for the tape. No more sticky adhesive devices. And no more concerns for the security and safety of your patient's airway. Now enjoy the speed, simplicity and protection of STRAPEZE.**

**Strap versus tape**

Tape kinks, binds, and often loses its adhesive qualities under operating conditions. STRAPEZE, as its name implies, is a strap made of 100% non-allergenic Velfoam II®, a very durable and lightweight material with a foam core sandwiched between outer layers of soft, synthetic lambs-wool.

**So easy to apply**

The STRAPEZE "one-step" fastening concept brings a new measure of assurance and security to endotracheal tube placement. And there's nothing else like it for ease of use. You simply attach one end of STRAPEZE to the tube, slip the strap behind the patient's neck, loop around tube and fasten with the Velcro tab back onto the strap's velvety surface. Job finished!



**Stays put—or it's not STRAPEZE!**

Now you can forget about accidental extubations or bronchial intubations. STRAPEZE ensures precise and positive positioning of the tube. Where you put it, is where it stays. Which means the tube won't pull out, and it won't push down. Needless to say, such assurances can be a lifesaver.

**Another quality product from ProTechPacific**

STRAPEZE was designed to answer the demanding needs of today's medical professional. Its innovative simplicity erases the tedium and uncertainty of performing an important task. And its specialized function is another example of ProTech Pacific's ongoing commitment to your profession. STRAPEZE. New convenience. New security. New comfort. And, for all these assurances, very inexpensive. For the comfort of the intubated patient, STRAPEZE is here to stay. Because it *stays put.*

*U.S. Patents pending*

**ProTechPacific**

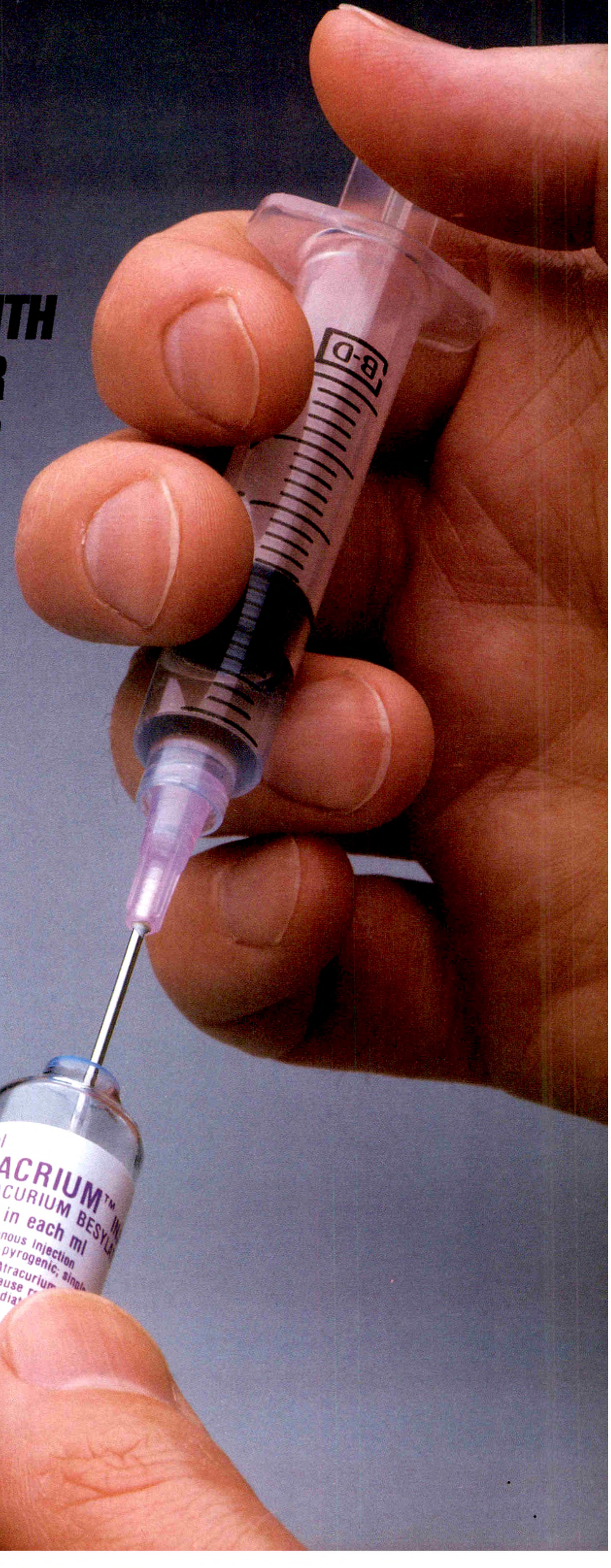
*1221 Andersen Drive*
*San Rafael, California 94901*
*Call Toll Free: 800/227-0517*
*In Calif. 415/459-0745*

*Manufacturers of Protective Medical Products*

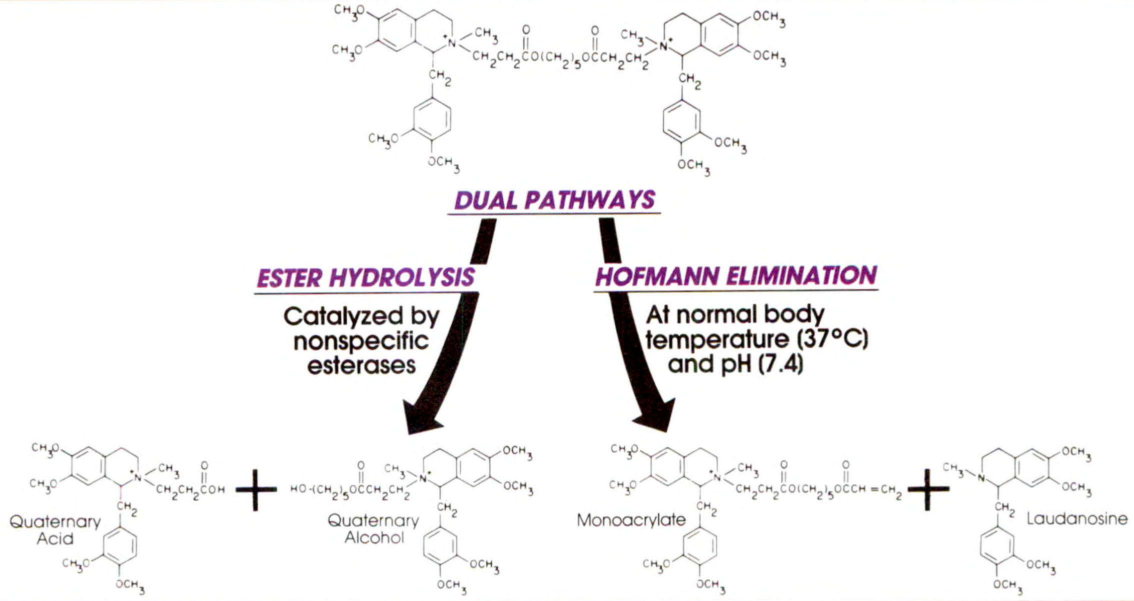
Burroughs Wellcome Co. presents

# AN INTERMEDIATE-ACTING SURGICAL MUSCLE RELAXANT WITH FEW CARDIOVASCULAR EFFECTS AND GREATER CONTROLLABILITY

## NO MIXING NEEDED!



# UNIQUE METABOLISM PROVIDES BETTER PREDICTABILITY, ALLOWING BETTER CONTROL



☐ *Tracrium® Injection (atracurium besylate) is inactivated by two nonoxidative pathways that are not dependent on kidney or liver function:*

*1 Hofmann elimination—a nonenzymatic process that occurs at physiologic temperature and pH*

*2 Ester hydrolysis—catalyzed by nonspecific esterases; normal levels of plasma cholinesterase are not required*

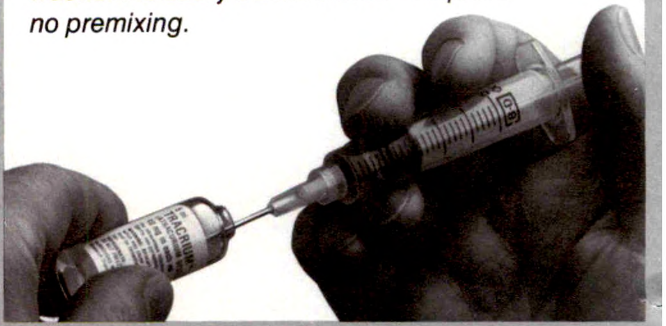
*These attributes make Tracrium a more flexible surgical muscle relaxant—it may be tailored to a wide variety of surgical cases.*

*"Atracurium has the special feature of being broken down to inactive products by the Hofmann elimination reaction. This means that the active drug can be removed from the biophase by other means not totally dependent on enzyme action, redistribution or excretion."*[1]

*"At present, no other available muscle relaxant undergoes this kind of degradation at physiologic pH."*[2]

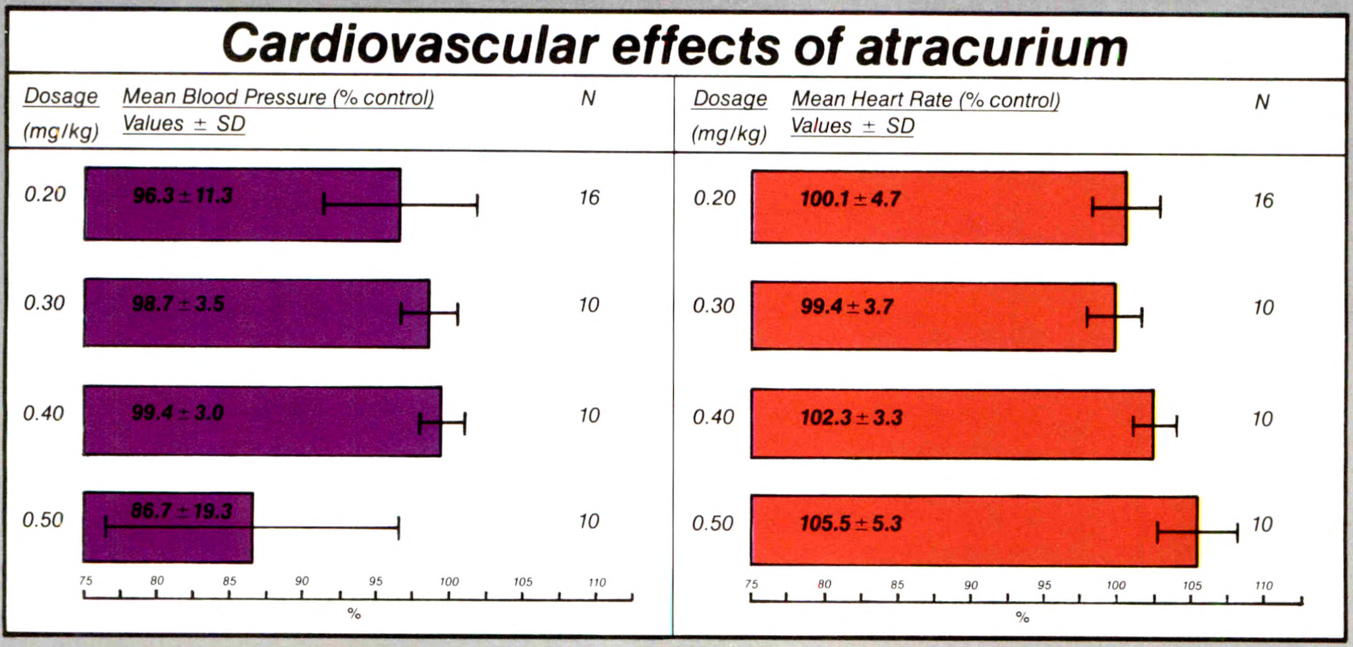
## Convenient and Ready to Use

*Tracrium is easily administered—requires no premixing.*



## Few Cardiovascular Effects at Recommended Dosages

☐ *Tracrium® (atracurium besylate) produces virtually no clinically significant cardiovascular hemodynamic changes when administered at recommended dosage levels—a significant benefit in patients with compromised cardiac ability or cardiac risk.*



*Adapted from Basta et al.*[3]

## No Cumulative Effects Upon Recovery, After Multiple Doses

☐ *Repeated equipotent doses of Tracrium, administered at equal points of recovery, have no cumulative effect on recovery time*

☐ *Once recovery begins, it is relatively rapid and independent of dose*

☐ *This means that you do not have to calculate progressively smaller doses for repeat administration, and that recovery is more consistent and predictable*

*"One patient received 12 successive doses of atracurium after recovering completely from the initial dose, yet the 25%-75% recovery times were 10.0 and 12.2 min, respectively. This may indicate that atracurium is not cumulative. . . ."*[1]

## Minimal Histamine Release

☐ *Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine*

☐ *Clinically significant histamine release occurs well within the clinical dosage range (at $ED_{95}$) for curare, at the upper limits of the clinical dosage range (at 2 × $ED_{95}$) for metocurine and outside the clinical dosage range (at 3 × $ED_{95}$) for atracurium*[4]

☐ *The lack of hemodynamic changes due to Tracrium suggests minimal histamine release*

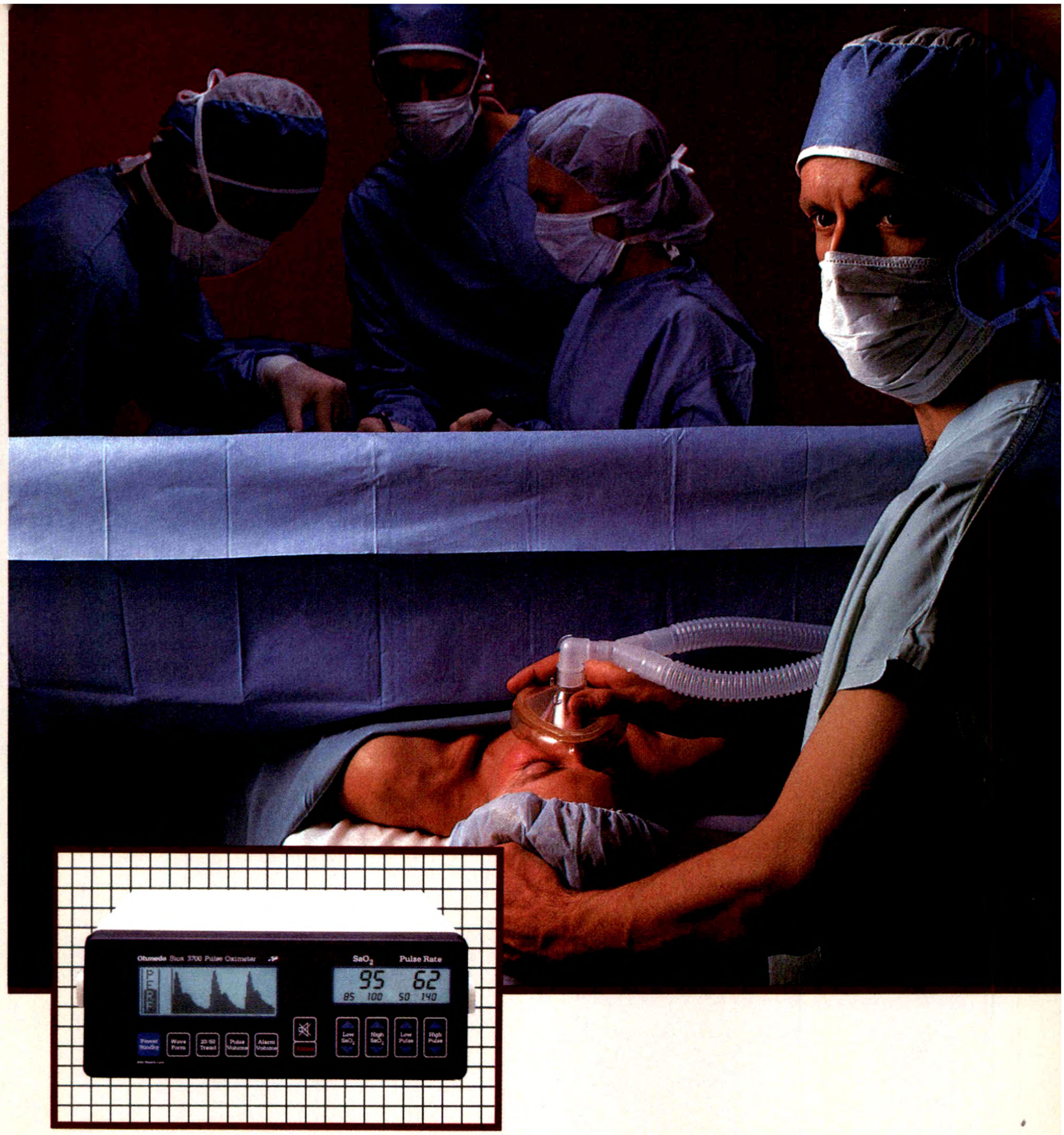
*Please see brief summary of prescribing information on the following page.*

*REFERENCES:*

1. *Ali HH, Savarese JJ, Basta SJ, et al: Clinical pharmacology of atracurium: A new intermediate acting nondepolarizing relaxant. Seminars in Anesthesia 1982; 1:57-62.*
2. *Katz RL, Stirt J, Murray AL, et al: Neuromuscular effects of atracurium in man. Anesth Analg 1982; 61:730-734.*
3. *Basta SJ, Ali HH, Savarese JJ, et al: Clinical pharmacology of atracurium besylate (BW 33A): A new non-depolarizing muscle relaxant. Anesth Analg 1982; 61:723-729.*
4. *Basta SJ, Savarese JJ, Ali HH, et al: Histamine-releasing potencies of atracurium besylate (BW 33A), metocurine, and d-tubocurarine. Anesthesiology 1982;57:A261.*

**TRACRIUM® INJECTION**
(atracurium besylate)

*Copr. ©1984 Burroughs Wellcome Co. All rights reserved.*



# The New Ohmeda Biox 3700 Pulse Oximeter. Because hypoxemia is an $SaO_2$ problem.

**Why oximetry.**

A drop in arterial blood oxygenation ($SaO_2$) calls for quick and effective action. Especially in anesthesia, where oxygen starvation can jeopardize your patient's safety. Only oximetry provides the means for direct and efficient monitoring of $SaO_2$—giving you the crucial time needed to prevent clinical complications.

**Why Ohmeda.**

Now, the Ohmeda Biox 3700 Pulse Oximeter helps you in the prompt detection of hypoxemia. Continuous, reliable and non-invasive, only the 3700 shows you a plethysmographic waveform—plus $SaO_2$ trending of the past 20 or 60 minutes. Both visual and audible indicators continuously inform you of your patient's $SaO_2$ condition as you work. The 3700 has a battery backup, for easy transport and emergency power support. And its three types of probes make the 3700 ideally suited for any patient.

So, prevent minor procedures from becoming major hypoxic crises. Rely on the Ohmeda Biox 3700. It's the confident response to the critical demands of anesthesia.

**Ohmeda**

Ohmeda
4765 Walnut Street
Boulder, Colorado 80301 1 800 652 2469
A Division of The BOC Group, Inc.
**BOC Health Care**

# THROUGHOUT THE PERI-

## to relieve excessive anxiety

### Rapid relief of anxiety and apprehension

Anxiety is an extremely common reaction to the stress of anesthesia and surgery. Often at its most acute stage in the minutes just before induction, anxiety may even affect the outcome of the surgical procedure.[1]

To relieve anxiety promptly and predictably, no agent is more effective than Injectable Valium® (diazepam/Roche) I.V.

Within minutes after an I.V. injection,[2,3] most patients become noticeably calmer, sedated yet easily aroused if necessary. This response is prompt and predictable—just the kind you want in the anxious moments before surgery.

**Rarely compromises cardiac or respiratory function** Injectable Valium rarely produces clinically significant alterations in basal circulatory parameters.[4-6] In a series of 16,000 patients, apnea occurred in only three patients given Injectable Valium intravenously.[7] However, caution should be taken when administering the agent to elderly or debilitated patients with limited pulmonary reserve. Resuscitative equipment should be available for all patients, and narcotics should be reduced by one-third or more; in some cases they may be eliminated.

Copyright © 1985
by Roche Products Inc.
All rights reserved.

# OPERATIVE PERIOD

## to diminish recall

**Diminishes recall of unpleasant or painful procedures** When patients have vivid memories of invasive procedures, they may be less than willing to undergo such procedures again, even if they are medically necessary.[8,9] Recall of procedures such as endotracheal intubation can be diminished by the rapid-acting amnesic effect of Injectable Valium (diazepam/Roche) I.V. Anterograde amnesia usually begins within three minutes after a single I.V. injection, peaks within ten minutes and lasts for 20 to 60 minutes.[3,10,11]

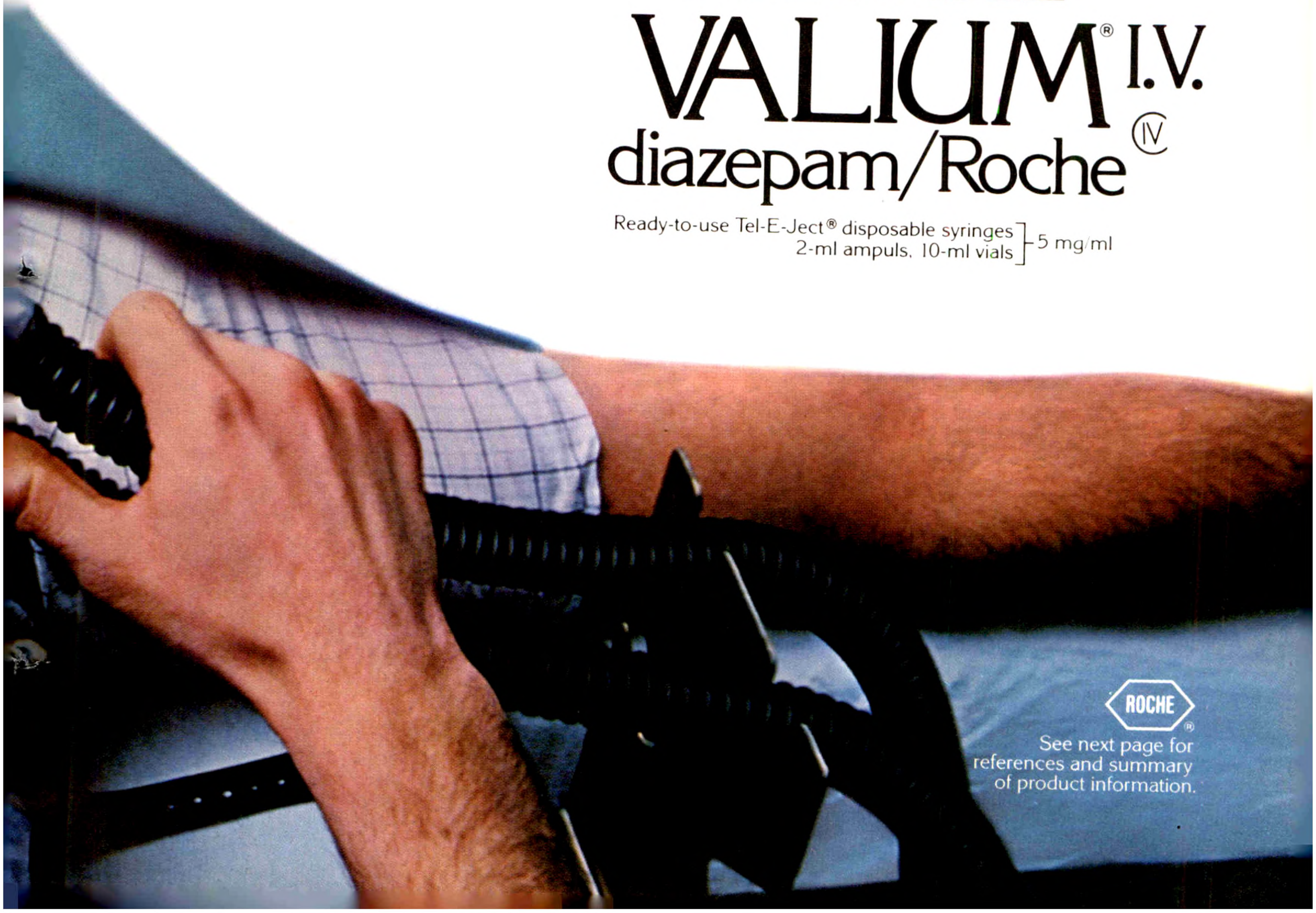
This predictable pattern of action distinguishes Injectable Valium from other agents that can produce amnesia and sedation. Other agents can take 15 to 30 minutes to achieve the desired effect, and the effects may last for 24 hours or more.[2] However, patients should be warned about driving or performing other potentially dangerous activities after receiving Injectable Valium.

**Easily titrated for desired effect** The compact 10-mg prefilled syringe makes individualized titration of Injectable Valium (diazepam/Roche) simple because there is convenient, easily readable milligram calibration on both sides of the barrel. And unlike other injectable agents, Injectable Valium needs no reconstitution before administration and no refrigeration during storage. Do not mix or dilute Valium with other drugs or solutions. Administer slowly in a large vein or through the infusion line as close to the vein insertion site as possible.

Injectable Valium. In a class by itself for rapidly relieving anxiety and diminishing recall.

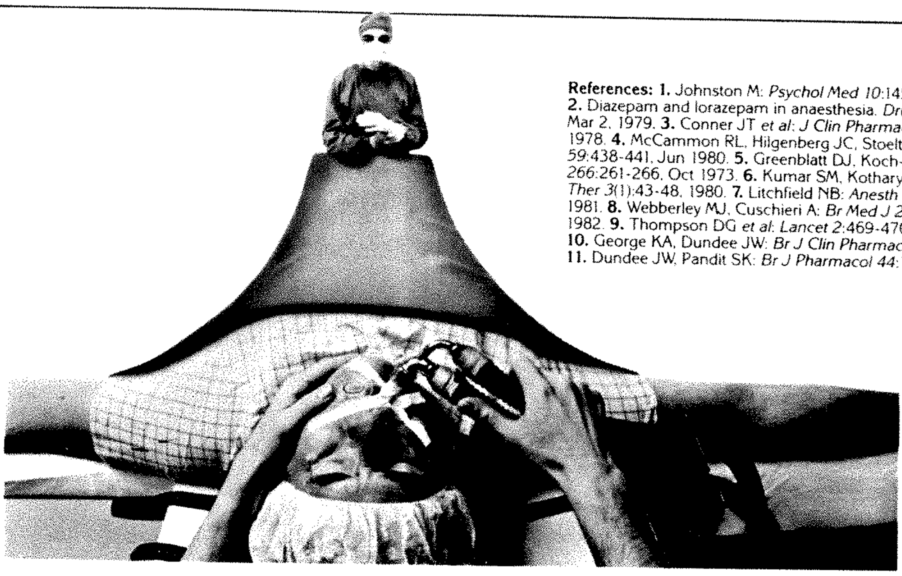
Prompt
Predictable
INJECTABLE
VALIUM® I.V.
diazepam/Roche Ⓘⓥ

Ready-to-use Tel-E-Ject® disposable syringes ⎤
2-ml ampuls, 10-ml vials ⎦ 5 mg/ml



ROCHE®

See next page for references and summary of product information.



**References: 1.** Johnston M: *Psychol Med 10*:145-152, Feb 1980. **2.** Diazepam and lorazepam in anaesthesia. *Drug Ther Bull 17*:19-20, Mar 2, 1979. **3.** Conner JT *et al*: *J Clin Pharmacol 18*:285-292, May-Jun 1978. **4.** McCammon RL, Hilgenberg JC, Stoelting RK: *Anesth Analg 59*:438-441, Jun 1980. **5.** Greenblatt DJ, Koch-Weser J: *Am J Med Sci 266*:261-266, Oct 1973. **6.** Kumar SM, Kothary SP, Zsigmond EK: *Clin Ther 3*(1):43-48, 1980. **7.** Litchfield NB: *Anesth Prog 29*:11-17, Jan-Feb, 1981. **8.** Webberley MJ, Cuschieri A: *Br Med J 285*:251-252, Jul 24, 1982. **9.** Thompson DG *et al*: *Lancet 2*:469-470, Aug 30, 1980. **10.** George KA, Dundee JW: *Br J Clin Pharmacol 4*:45-50, Feb 1977. **11.** Dundee JW, Pandit SK: *Br J Pharmacol 44*:140-144, Jan 1972.

# INJECTABLE VALIUM® (diazepam/Roche) CIV

**Please consult complete product information, a summary of which follows:**

**Indications:** Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; tetanus; status epilepticus, severe recurrent seizures; adjunctively in anxiety, tension or acute stress reactions prior to endoscopic/surgical procedures; cardioversion.
**Contraindications:** Hypersensitivity; acute narrow angle glaucoma; may be used in patients with open angle glaucoma receiving appropriate therapy.
**Warnings:** *To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling and, rarely, vascular impairment when used I.V.: inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins, i.e., dorsum of hand or wrist; use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*
Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea; have resuscitative facilities available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least 1/3, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs.
As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).
Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status.
Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation after long use of excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after long, continuous use at high therapeutic levels. After extended therapy, gradually taper dosage.

> ***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations, as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for OB use.
Efficacy/safety not established in neonates (age 30 days or less); prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence; can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.
**Precautions:** Although promptly controlled, seizures may return; readminister if necessary; not recommended for long-term maintenance therapy.
If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam/Roche), *i.e.*, phenothiazines, narcotics, barbiturates, MAO inhibitors, antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.
The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.
**Adverse Reactions:** Drowsiness, fatigue, ataxia, venous thrombosis/phlebitis at injection site, confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo, constipation, nausea, incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat and chest have been reported in peroral endoscopic procedures.
Isolated reports of neutropenia, jaundice; periodic blood counts, liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.
**Dosage:** Usual initial dose in older children and adults is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.)
For dosages in infants and children see below; have resuscitative facilities available.
*I.M. use: by deep injection into the muscle.*
*I.V. use: inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins, i.e., dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*
Moderate anxiety disorders and symptoms of anxiety, 2 to 5 mg I.M. or I.V. and severe anxiety disorders and symptoms of anxiety, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcohol withdrawal, 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary. Muscle spasm, in adults, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses): in children, *administer I.V. slowly;* for tetanus in infants over 30 days of age, 1 to 2 mg I.M. or I.V., repeat every 3 to 4 hours if necessary; in children 5 years or older, 5 to 10 mg repeated every 3 to 4 hours as needed. Respiratory assistance should be available.
Status epilepticus, severe recurrent convulsive seizures (I.V. route preferred), 5 to 10 mg adult dose administered slowly, repeat at 10- to 15-minute intervals up to 30 mg maximum. Repeat in 2 to 4 hours if necessary, keeping in mind possibility of residual active metabolites. Use caution in presence of chronic lung disease or unstable cardiovascular status. Infants (over 30 days) and children (under 5 years), 0.2 to 0.5 mg slowly every 2 to 5 min., up to 5 mg (I.V. preferred). Children 5 years plus, 1 mg every 2 to 5 min., up to 10 mg (slow I.V. preferred); repeat in 2 to 4 hours if needed. EEG monitoring may be helpful.
In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg I.V. within 5 to 10 minutes prior to procedure.
Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.
**Management of Overdosage:** Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of limited value.
**Supplied:** Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1 and 10; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

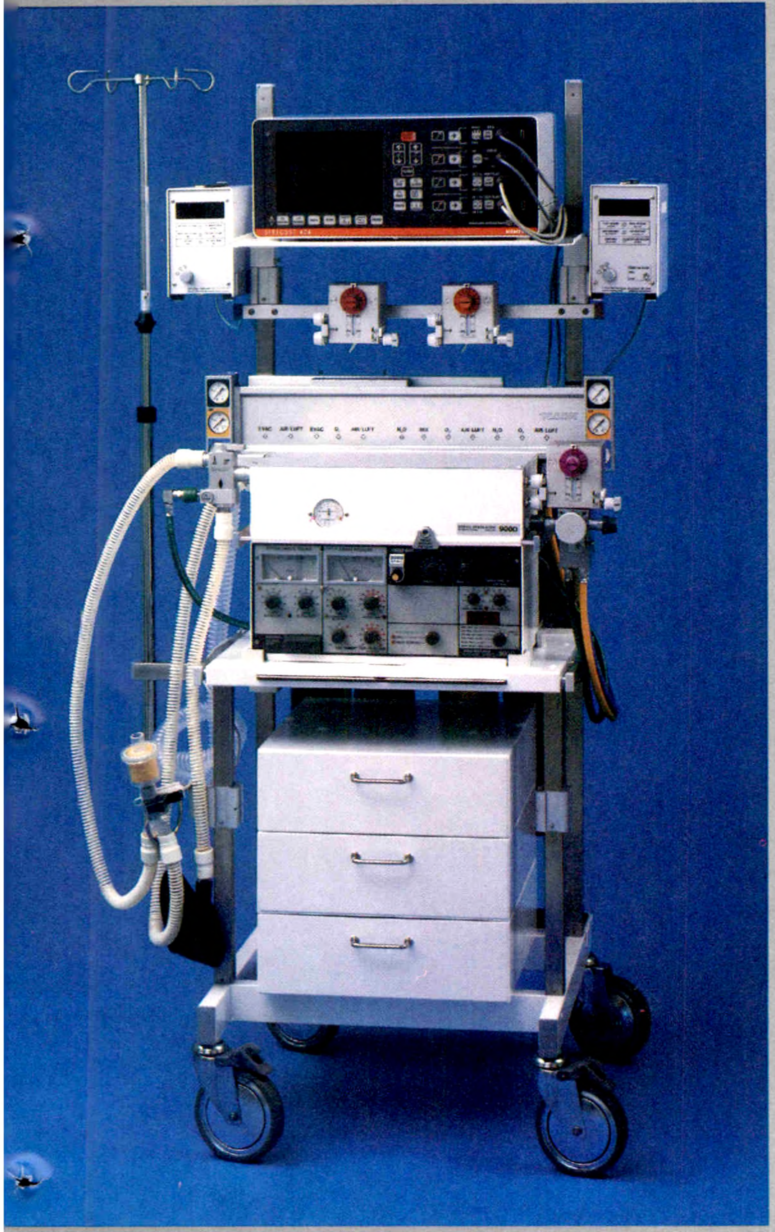
ROCHE®

Manufactured by Hoffmann-La Roche Inc.
Nutley, New Jersey 07110
Distributed by Roche Products Inc.
Manati, Puerto Rico 00701

**SIEMENS**

Introducing the Servo Anesthesia System

# The advanced anesthesia system for pediatric and adult patients.



Now there's one highly versatile anesthesia system designed for routine and critical care cases involving pediatric as well as adult patients. It's the new Servo Anesthesia System from Siemens. Compact and modular in design, the system is human-engineered for ease of operation and highly accurate control...plus maximum safety.

**New versatility and efficiency in the OR**
The system utilizes our Servo Ventilator, offering the most advanced technology available for both volume-controlled and pressure-supported anesthesia applications. A new ventilation mode, pressure support, enables patients to breathe spontaneously with the assistance of a predetermined pressure. The system continuously monitors all important functions and provides instantaneous readings and audible/visual alarms.

**Advanced monitoring interface**
The Servo Anesthesia System interfaces with a broad range of exclusive, innovative monitoring systems, including the $CO_2$ Analyzer 930, the Lung Mechanics Calculator 940 and the Sirecust 404.

**New ease of maintenance**
You're assured of quality performance with a minimum of maintenance. The system requires only minimal servicing; the costs are extraordinarily low. And best of all, most maintenance is easily performed right on site by members of your own staff. No costly off-site service!

And you're further assured of immediate professional assistance, if necessary, from your Siemens sales and service representatives. It's all part of the Siemens commitment to superior products and systems for healthcare professionals and their patients.

For further information, contact
Siemens-Elema Ventilator Systems,
2360 No. Palmer Dr., Schaumburg,
Illinois 60195—(312) 397-5975, or
call toll-free 1-800-323-1281.

**Siemens...a pioneer in innovative healthcare systems.**

Siemens-Elema Ventilator Systems,
2360 No. Palmer Dr., Schaumburg, IL 60195
☐ Please send me information on Servo Anesthesia System.
Name
Institution
Address
City
State
Zip

MG/5820-009 WLM 174

In

# Reversal

of nondepolarizing
muscle relaxants,
don't look for what's better...
...look for what's best

# Regonol®

## (pyridostigmine bromide injection, USP)

when compared to neostigmine

☐ Clinically fewer side effects
☐ Significantly lower degree and incidence of:
  1) Bradycardia
  2) Salivation
  3) Gastrointestinal stimulation
☐ Wide margin of safety[1,2]

Organon
**Organon Pharmaceuticals**
A Division of Organon Inc.
West Orange, N.J. 07052

OR-5091

**Regonol** (pyridostigmine bromide injection USP)

**BRIEF SUMMARY**—(Please consult full package insert, enclosed in every package, before using Regonol)

**INDICATIONS**—Pyridostigmine bromide is useful as a reversal agent or antagonist to nondepolarizing muscle relaxants.

**CONTRAINDICATIONS**—Known hypersensitivity to anticholinesterase agents; intestinal and urinary obstructions of mechanical type.

**WARNINGS**—Pyridostigmine bromide should be used with particular caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Atropine should also be used with caution in patients with cardiac dysrhythmias. When large doses of pyridostigmine bromide are administered, as during reversal of muscle relaxants, prior or simultaneous injection of atropine sulfate is advisable. Because of the possibility of hypersensitivity in an occasional patient, atropine and antishock medication should always be readily available.

When used as an antagonist to nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance and there should be continuous patient observation. Satisfactory recovery may be defined by a combination of clinical judgement, respiratory measurements and observation of the effects of peripheral nerve stimulation. If there is any doubt concerning the adequacy of recovery from the effects of the nondepolarizing muscle relaxant, artificial ventilation should be continued until all doubt has been removed.

***Use in Pregnancy***—The safety of pyridostigmine bromide during pregnancy or lactation in humans has not been established. Therefore its use in women who are pregnant requires weighing the drug's potential benefits against its possible hazards to mother and child.

**ADVERSE REACTIONS**—The side effects of pyridostigmine bromide are most commonly related to overdosage and generally are of two varieties, muscarinic and nicotinic. Among those in the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and diaphoresis. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and weakness. Muscarinic side effects can usually be counteracted by atropine. As with any compound containing the bromide radical, a skin rash may be seen in an occasional patient. Such reactions usually subside promptly upon discontinuance of the medication. Thrombophlebitis has been reported subsequent to intravenous administration.

**DOSAGE AND ADMINISTRATION**—When pyridostigmine bromide is given intravenously to reverse the action of muscle relaxant drugs, it is recommended that atropine sulfate (0.6 to 1.2 mg) or glycopyrrolate in equipotent doses be given intravenously immediately prior to or simultaneous with its administration. Side effects, notably excessive secretions and bradycardia, are thereby minimized. Reversal dosages range from 0.1-0.25 mg/kg. Usually 10 or 20 mg. of pyridostigmine bromide will be sufficient for antagonism of the effects of the nondepolarizing muscle relaxants. Although full recovery may occur within 15 minutes in most patients, others may require a half hour or more. Satisfactory reversal can be evident by adequate voluntary respiration, respiratory measurements and use of a peripheral nerve stimulator device. It is recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. Once satisfactory reversal has been attained, recurarization has not been reported.

Failure of pyridostigmine bromide to provide prompt (within 30 minutes) reversal may occur, e.g., in the presence of extreme debilitation, carcinomatosis, or with concomitant use of certain broad spectrum antibiotics or anesthetic agents, notably ether. Under these circumstances ventilation must be supported by artificial means until the patient has resumed control of his respiration.

**HOW SUPPLIED**—Regonol is available in:
5 mg/ml: 2 ml. ampuls—boxes of 25—NDC-0052-0460-02
5 ml. vials—boxes of 25—NDC-0052-0460-05

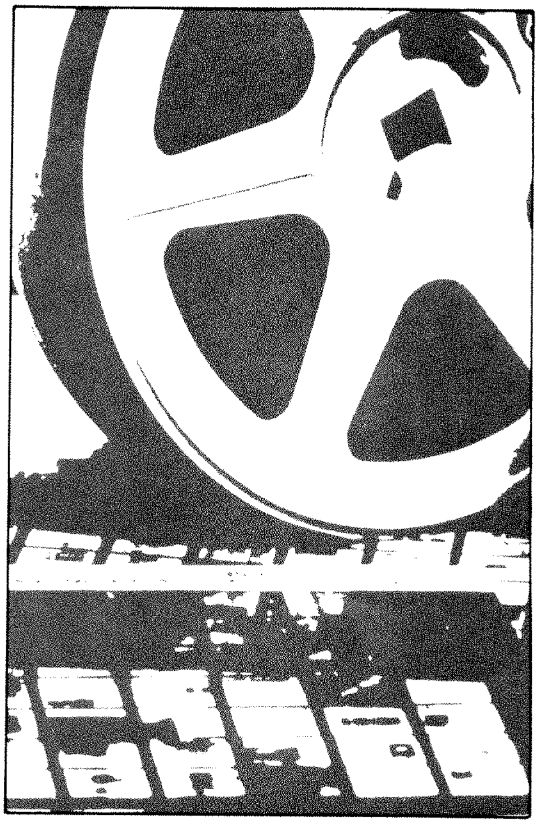
**REFERENCES:**
1. Gyermek L: Clinical studies on the reversal of the neuromuscular blockade produced by pancuronium bromide. 1. The effects of glycopyrrolate and pyridostigmine. *Curr Ther Res* 18:377-386, 1975.
2. Ravin MB: Pyridostigmine as an antagonist of d-tubocurarine-induced and pancuronium-induced neuromuscular blockade. *Anesth Analg—Curr Res* 54:317-321, 1975.

Organon

**Organon Pharmaceuticals**
**A Division of Organon Inc.**
**West Orange, N.J. 07052**

OR-5091

**This Publication is available in Microform.**



**University Microfilms International**

Please send additional information
for ______________________
(name of publication)
Name______________________
Institution______________________
Street______________________
City______________________
State______________ Zip______________

300 North Zeeb Road
Dept. P.R.
Ann Arbor, Mi. 48106

# ANNOUNCING: The new, easily identifiable, economical, shatter-resistant, 10 ml, multiple-dose vial

(100 mg atracurium besylate per vial).

Multiple-dose vials can reduce the amount of Tracrium subject to waste by as much as 22% when compared to ampules!*

*Data on file, Burroughs Wellcome Co.

**TRACRIUM**® INJECTION
(atracurium besylate)

Wellcome
**Burroughs Wellcome Co.**
Research Triangle Park
North Carolina 27709

Copr. © 1985 Burroughs Wellcome Co. All rights reserved. 85TRA10

# Marcaine® Spinal

## bupivacaine HCl, USP, 0.75%
## with dextrose, USP, 8.25% injection

**PLEASE CONSULT FULL PRESCRIBING INFORMATION: A SUMMARY FOLLOWS:**

**CONTRAINDICATIONS:** MARCAINE Spinal is contraindicated in patients with a known hypersensitivity to it or to any local anesthetic agent of the amide-type. The following conditions preclude the use of spinal anesthesia: (1) Severe hemorrhage, severe hypotension, or shock and arrhythmias, such as complete heart block, which severely restrict cardiac output; (2) Local infection at the site of proposed lumbar puncture; (3) Septicemia.

WARNINGS: LOCAL ANESTHETICS SHOULD ONLY BE EMPLOYED BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES WHICH MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED, AND THEN ONLY AFTER INSURING THE **IMMEDIATE** AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY RESUSCITATIVE EQUIPMENT, AND THE PERSONNEL RESOURCES NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES. (See also ADVERSE REACTIONS and PRECAUTIONS.) DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST, AND, POSSIBLY, DEATH.

Spinal anesthetics should not be injected during uterine contractions, because spinal fluid current may carry the drug further cephalad than desired.

A free flow of cerebrospinal fluid while performing spinal anesthesia indicates entry into the subarachnoid space. Aspiration should be performed before the anesthetic is injected to confirm entry into the subarachnoid space and to avoid intravascular injection.

MARCAINE solutions containing epinephrine or other vasopressors should not be used concomitantly with ergot-type oxytocic drugs, because severe, persistent hypertension may occur. MARCAINE solutions containing a vasoconstrictor such as epinephrine should be used cautiously in patients receiving monoamine oxidase inhibitors (MAOI) or antidepressants of the triptyline or imipramine types, because severe prolonged hypertension may result.

Administration of MARCAINE to patients younger than 18 years is not recommended, nor is the mixing or the prior or intercurrent use of any other local anesthetic with MARCAINE because of insufficient data on the clinical use of such mixtures.

**PRECAUTIONS: General:** The safety and effectiveness of spinal anesthetics depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use. (See WARNINGS and ADVERSE REACTIONS.) The patients should have IV fluids running via an indwelling catheter to assure a functioning intravenous pathway. The lowest dosage of local anesthetic that results in effective anesthesia should be used. Aspiration for blood should be performed before injection and injection should be made slowly. Tolerance varies with the status of the patient. Elderly patients and acutely ill patients may require reduced doses. Reduced doses may also be indicated in patients with increased intra-abdominal pressure (including obstetrical patients), if otherwise suitable for spinal anesthesia.

Cardiovascular and respiratory vital signs and the patient's state of consciousness after local anesthetic injection should be constantly and carefully monitored. Restlessness, anxiety, incoherent speech, light-headedness, numbness, and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of central nervous system toxicity.

Spinal anesthetics should be used cautiously in patients with severe disturbances of cardiac rhythm, shock or heart block.

Sympathetic blockade during spinal anesthesia may result in peripheral vasodilation and hypotension, the extent depending on the number of dermatomes blocked. Blood pressure should be carefully monitored especially in the early phases of anesthesia. Hypotension may be controlled by vasoconstrictors in dosages depending on the severity of hypotension and response of treatment. The level of anesthesia should also be carefully monitored because it is not always controllable in spinal techniques.

Because the liver metabolizes amide-type local anesthetics such as MARCAINE, these drugs, especially repeat doses, should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease are at a greater risk of developing toxic plasma concentrations. Local anesthetics should also be used cautiously in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs. However, dosage recommendations for spinal anesthesia are much lower than those in other major blocks; most experience regarding hepatic and cardiovascular disease dose-related toxicity is derived from these other major blocks.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are used in patients during or following the administration of potent inhalation agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents on the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be considered.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. It is not known whether amide-type local anesthetics trigger this reaction, and since the need for supplemental general anesthesia cannot be predicted in advance, a standard protocol for management should be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure, and metabolic acidosis may precede temperature elevation. Successful outcome depends on early diagnosis, prompt discontinuance of the suspect triggering agent(s) and institution of treatment, including oxygen therapy, indicated supportive measures and dantrolene. (Consult dantrolene sodium package insert before using.)

The following conditions may preclude the use of spinal anesthesia, depending on the physician's evaluation of the situation and ability to deal with possible complications or complaints: (1) Preexisting diseases of the central nervous system, such as those resulting from pernicious anemia, poliomyelitis, syphilis, tumor; (2) Hematological disorders predisposing to coagulopathies or patients on anticoagulant therapy. Trauma to a blood vessel during the conduct of spinal anesthesia may, in some instances, result in uncontrollable central nervous system hemorrhage or soft tissue hemorrhage; (3) Chronic backache and preoperative headache; (4) Hypotension and hypertension; (5) Technical problems (persistent paresthesias or bloody tap); (6) Arthritis or spinal deformity; (7) Extremes of age; (8) Psychosis or other causes of poor cooperation by the patient.

**Information for Patients:** Patients should be informed that they may experience temporary loss of sensation and motor activity, usually in the lower half of the body, following proper administration of spinal anesthesia. Also, when appropriate, the physician should discuss other information including adverse reactions in the MARCAINE Spinal package insert.

**Clinically Significant Drug Interactions:** Local anesthetic solutions containing epinephrine or norepinephrine administered to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe, prolonged hypertension. Concurrent use of these agents should generally be avoided but, when necessary, careful patient monitoring is essential.

Concurrent administration of vasopressor drugs and of ergot-type oxytocic drugs may cause severe persistent hypertension or cerebrovascular accidents.

Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine.

**Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Long-term studies in animals of most local anesthetics including bupivacaine to evaluate carcinogenic potential have not been conducted. Mutagenic potential or the effect on fertility have not been determined. There is no evidence from human data that MARCAINE Spinal may be carcinogenic, or mutagenic or that it impairs fertility.

**Pregnancy Category C:** Decreased pup survival in rats and an embryocidal effect in rabbits have been observed when bupivacaine hydrochloride was administered in doses comparable to 230 and 130 times respectively the maximum recommended human spinal dose. There are no adequate and well-controlled studies in pregnant women of bupivacaine's effect on the developing fetus. Bupivacaine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. This does not exclude the use of MARCAINE Spinal at term for obstetrical anesthesia. (See **Labor and Delivery.**)

**Labor and Delivery:** Spinal anesthesia has a recognized use during labor and delivery. Bupivacaine hydrochloride, when administered properly, via the epidural route in doses 10 to 12 times the amount used in spinal anesthesia has been used for obstetrical analgesia and anesthesia without evidence of adverse effects on the fetus.

Regional anesthesia has produced maternal hypotension. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal heart rate should be monitored continuously and electronic fetal monitoring is highly advisable.

It is extremely important to avoid aortocaval compression by the gravid uterus during administrations of regional block to parturients. To do this, the patient must be maintained in the left lateral decubitus position or a blanket roll or sandbag may be placed beneath the right hip and the gravid uterus displaced to the left.

Spinal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. Spinal anesthesia has also been reported to prolong the second stage of labor by removing the parturient's reflex urge to bear down or by interfering with motor function. Obstetrical anesthesia may increase the need for forceps assistance.

The use of some local anesthetic drug products during labor and delivery may result in diminished muscle strength and tone for the first day or two of life. This has not been reported with bupivacaine.

Cardiac arrest has been reported during use of MARCAINE 0.75% solution for epidural anesthesia in obstetrical patients. The MARCAINE hydrochloride package insert for epidural, nerve block, etc, discusses this problem. These cases are compatible with systemic toxicity following unintended intravascular injection of the much larger doses recommended for epidural anesthesia and have not occurred within the dose range of bupivacaine hydrochloride 0.75% recommended for obstetrical spinal anesthesia. The 0.75% concentration of MARCAINE is therefore not recommended for obstetrical epidural anesthesia. MARCAINE Spinal (bupivacaine HCl 0.75% with dextrose 8.25%) is recommended for spinal anesthesia in obstetrics.

**Nursing Mothers:** It is not known whether local anesthetic drugs are excreted in human milk; therefore, caution should be exercised when local anesthetics are administered to a nursing woman.

**Pediatric Use:** Until further experience is gained in patients younger than 18 years, administration of MARCAINE Spinal in this age group is not recommended.

**ADVERSE REACTIONS:** Reactions to bupivacaine are characteristic of those associated with other amide-type local anesthetics. The most commonly encountered acute adverse experiences following spinal anesthesia are hypotension due to loss of sympathetic tone and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia. These may lead to cardiac arrest if untreated. In addition, dose-related convulsions and cardiovascular collapse may result from diminished tolerance, rapid absorption from the injection site, or from unintentional intravascular injection of a local anesthetic solution. Factors influencing plasma protein binding, such as acidosis, systemic diseases which alter protein production, or competition of other drugs for protein binding sites, may diminish individual tolerance.

**Respiratory System:** Respiratory paralysis or underventilation may result from upward extension of the level of spinal anesthesia and may lead to secondary hypoxic cardiac arrest if untreated. Preanesthetic medication, intraoperative analgesics and sedatives, as well as surgical manipulation may contribute to underventilation. This will usually occur within minutes of the injection of spinal anesthetic solution, but because of differing maximal onset times, intercurrent drug use, and surgical manipulation, it may occur at any time during surgery or the immediate recovery period.

**Cardiovascular System:** Hypotension due to loss of sympathetic tone is a commonly encountered extension of the clinical pharmacology of spinal anesthesia. This is more commonly observed in patients with shrunken blood and interstitial fluid volumes, cephalad spread of the local anesthetic and/or mechanical obstruction of venous return. Nausea and vomiting are frequently associated with hypotensive episodes following the administration of spinal anesthesia. High doses, or inadvertent intravascular injection, may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, bradycardia, heart block, ventricular arrhythmias and possibly cardiac arrest. (See WARNINGS, PRECAUTIONS, and OVERDOSAGE sections.)

**Central Nervous System:** Respiratory paralysis or underventilation secondary to cephalad spread of the level of spinal anesthesia (see Respiratory System) and hypotension for the same reason (see Cardiovascular System) are the two most commonly encountered central nervous system-related adverse observations which demand immediate countermeasures.

High doses, or inadvertent intravascular injections may lead to high plasma levels and related central nervous system toxicity characterized by excitement and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest.

**Neurologic:** Adverse neurologic reactions associated with the use of local anesthetics may be related to the total dose of local anesthetic administered and also depend on the particular drug used, the route of administration and the physical status of the patient. Many effects may be related to local anesthetic techniques, with or without a contribution from the drug.

Neurologic effects following spinal anesthesia may include loss of perineal sensation and sexual function; persistent anesthesia, paresthesia, weakness and paralysis of the lower extremities and loss of sphincter control all of which may have slow, incomplete or no recovery; hypotension; high or total spinal block; urinary retention; headache; backache; septic meningitis; meningismus; arachnoiditis; slowing of labor, increased incidence of forceps delivery; shivering; cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid; fecal and urinary incontinence.

**Allergic:** Allergic-type reactions are rare and may occur as a result of sensitivity to the local anesthetic. These reactions include urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly anaphylactoid-like symptomatology (including severe hypotension). Cross-sensitivity among members of the amide-type local anesthetic group has been reported.

**Other:** Nausea and vomiting may occur during spinal anesthesia.

**OVERDOSAGE:** Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use or to underventilation (and perhaps apnea) secondary to upward extension of spinal anesthesia. Hypotension is commonly encountered during the conduct of spinal anesthesia due to relaxation of sympathetic tone or contributory mechanical obstruction of venous return.

**Management of Local Anesthetic Emergencies:** The first consideration is prevention through careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic injection. Administer oxygen at the first sign of change.

*The first step in managing systemic toxic reactions, as well as underventilation or apnea due to a high or total spinal is to* ***immediately*** *establish and maintain a patent airway and effective assisted or controlled ventilation with 100% oxygen with a delivery system capable of permitting immediate positive airway pressure by mask.* This may prevent convulsions if they have not already occurred.

If necessary, use drugs to control convulsions. A 50 mg to 100 mg bolus IV injection of succinylcholine will paralyze the patient without depressing central nervous or cardiovascular systems and facilitate ventilation. A bolus IV dose of 5 mg to 10 mg of diazepam or 50 mg to 100 mg of thiopental will permit ventilation and counteract central nervous system stimulation, but these drugs also depress central nervous system, respiratory and cardiac function, add to postictal depression and may result in apnea. Intravenous barbiturates, anticonvulsant agents, or muscle relaxants should only be administered by those familiar with their use. Immediately after instituting these ventilatory measures, the adequacy of the circulation should be evaluated. Supportive treatment of circulatory depression may require administration of intravenous fluids, and when appropriate, a vasopressor dictated by the clinical situation.

Hypotension due to sympathetic relaxation may be managed with intravenous fluids, in an attempt to relieve mechanical obstruction of venous return or by using vasopressors and, if indicated, by giving plasma expanders or whole blood.

Endotracheal intubation, employing drugs and techniques familiar to the physician, may be indicated after initial administration of oxygen by mask if difficulty is encountered in maintaining a patent airway or if prolonged ventilatory (assisted or controlled) support is indicated.

Recent clinical data from patients experiencing local anesthetic-induced convulsions demonstrated rapid development of hypoxia, hypercarbia, and acidosis with bupivacaine within a minute of the onset of convulsions. These observations suggest that oxygen consumption and carbon dioxide production are greatly increased during local anesthetic convulsions and emphasize the importance of immediate and effective ventilation with oxygen which may avoid cardiac arrest.

If not treated immediately, convulsions with simultaneous hypoxia, hypercarbia, and acidosis plus myocardial depression from the direct effects of the local anesthetic may result in cardiac arrhythmias, bradycardia, asystole, ventricular fibrillation, or cardiac arrest. Respiratory abnormalities, including apnea, may occur. Underventilation or apnea due to a high or total spinal may produce these same signs and also lead to cardiac arrest if ventilatory support is not instituted. If cardiac arrest occurs, standard cardiopulmonary resuscitative measures should be instituted and maintained for a prolonged period if necessary. Recovery has been reported after prolonged resuscitative efforts.

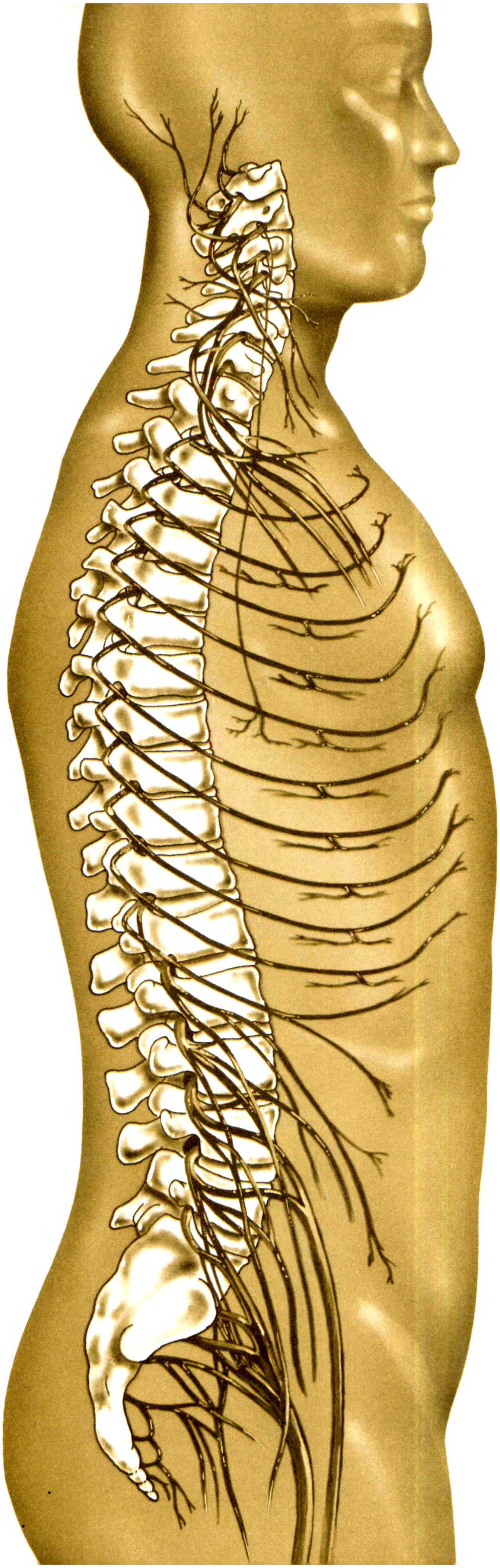
The supine position is dangerous in pregnant women at term because of aortocaval compression by the gravid uterus. Therefore, during treatment of systemic toxicity, maternal hypotension or fetal bradycardia following regional block, the parturient should be maintained in the left lateral decubitus position if possible, or manual displacement of the uterus off the great vessels be accomplished.

The mean seizure dosage of bupivacaine in rhesus monkeys was found to be 4.4 mg/kg with mean arterial plasma concentration of 4.5 mcg/mL. The intravenous and subcutaneous $LD_{50}$ in mice is 6 mg/kg to 8 mg/kg and 38 mg/kg to 54 mg/kg respectively.

**Composition of MARCAINE Spinal Solutions:** Each 1 mL of MARCAINE Spinal contains 7.5 mg bupivacaine hydrochloride and 82.5 mg dextrose. The pH of this solution is adjusted between 4.0 and 6.5 with sodium hydroxide or hydrochloric acid. The specific gravity of MARCAINE Spinal is between 1.030 and 1.035 at 25°C, and 1.03 at 37°C. MARCAINE Spinal does not contain any preservatives.

Winthrop-Breon

**WINTHROP-BREON LABORATORIES**
Division of Sterling Drug Inc.
New York, NY 10016



# Introducing a reliable anesthetic for spinal anesthesia

## Few spinal anesthetic failures

New Marcaine® Spinal offers the advantage of dependable and profound anesthesia for a wide variety of surgical and obstetrical procedures. **MARCAINE** Spinal in a dose of 7.5 mg had only one anesthetic failure in 121 patients.*[1]

## "...reliable local anesthetic solution for spinal anesthesia."[1]

- Rapid onset—within one minute
- Long duration—two to three hours
- Premixed hyperbaric solution
- No added bisulfites

## Marcaine® *Spinal*

(bupivacaine HCl, USP, 0.75% with dextrose, USP, 8.25% injection)

*in a dose of 7.5 mg for perineal and lower extremity surgery

*Winthrop-Breon*

**WINTHROP-BREON LABORATORIES**
Division of Sterling Drug Inc.
New York, NY 10016

**Reference:**
1. Moore DC: Spinal anesthesia: Bupivacaine compared with tetracaine. *Anesth Analg* 1980; 59:743-750.

©1984 Winthrop-Breon Laboratories

## Obituary

# Harold R. Griffith, MD, 1894–1985

> So far we have given Intocostrin to 25 patients. We have been so much impressed . . . that we believe this investigation should be continued.
>
> *Harold R. Griffith and G. Enid Johnson (1)*

Most of us could not imagine the practice of anesthesia without muscle relaxants. Thus it is no surprise that Griffith and Johnson's short, 2½ page description of the first use of curare in general anesthesia had such an impact on our specialty. Apart from being the first, its importance was clearly recognized by the editor of *Anesthesiology*, and it was published within six months of giving curare to the first of 25 patients. At last, muscle relaxation could be achieved without the risks of deep ether or cyclopropane or high spinal anesthesia. The stage was set for the development of balanced anesthesia so that the triad of sleep, analgesia, and relaxation could be achieved safely. Only then could surgeons contemplate major intrathoracic or abdominal operations in the sick patient.

The significance of the paper was of even greater importance to the growth of the specialty. Now that deliberate controlled ventilation was a normal accompaniment of anesthesia, the anesthesiologist learned to master his environment, allowing him access to developments of intensive care, respiratory medicine, and physiology. Within a decade, the techniques of anesthesia changed dramatically, pharmacologic development took a new course, and anesthesiologists became involved in the wider aspects of patient care. Life became more exciting.

Despite the revolution that Harold Griffith led, he remained a modest and retiring man. To him, it was equally important to campaign for the development of postanesthetic recovery rooms and intensive care units. As Professor and Chairman of the McGill Department of Anesthesia, he ensured that equal emphasis was given to research, education, and clinical care. To him, his greatest achievements were involved with the international fellowship of anesthesia, which culminated in his appointment as the Founder President of the World Federation of Societies of Anesthesiology.

During his life Dr. Griffith was the recipient of many awards. He was to become the only non-American to receive the Distinguished Service Award of the American Society of Anesthesiology. In 1974, he was made an Officer of the Order of Canada.

We remember a kind man and wise physician who changed the direction in which we walk.

David R. Bevan, MB, MRCP, FFARCS
*Department of Anesthesia*
*McGill University*
*Montreal, Canada*

### Reference

1. Griffith HR, Johnson GE. The use of curare in general anesthesia. Anesthesiology 1942;3:418–20.

© 1985 by the International Anesthesia Research Society

# Halothane and Isoflurane Do Not Decrease $PaO_2$ during One-Lung Ventilation in Intravenously Anesthetized Patients

Stephen N. Rogers, MD, and Jonathan L. Benumof, MD

ROGERS SN, BENUMOF JL. Halothane and isoflurane do not decrease $PaO_2$ during one-lung ventilation in intravenously anesthetized patients. Anesth Analg 1985;64:946–54.

*We examined the effect of the inhalational anesthetics halothane (H) and isoflurane (IF) on arterial oxygenation during one-lung ventilation. Twenty consenting patients who required thoracotomy and one-lung ventilation were initially anesthetized only with the intravenous agents, diazepam, fentanyl, pancuronium, metocurine, and infusions of either ketamine or methohexital. A double lumen endotracheal tube was inserted, and each patient's lungs were mechanically ventilated (two-lung ventilation, step 1) with 100% $O_2$ while the patient was in the lateral decubitus position. After the pleura was opened, the nondependent lung was collapsed while the dependent lung continued to be ventilated with 100% $O_2$. After serial $PaO_2$ measurements indicated achievement of stable one-lung ventilation conditions (step 2), intravenous anesthetic agents were discontinued, and either H ($n$ = 10) or IF ($n$ = 10) was administered (step 3) so that $PET_H = 7.70 \pm 0.61$ mm Hg and $PET_{IF} = 9.89 \pm 1.08$ mm Hg for more than 15 min; at the end of step 3, $Pa_H/PET_H = 0.82$ ($n = 5$), $Pa_{IF}/PET_{IF} = 0.75$ ($n = 5$), $P\bar{v}_H/PET_H = 0.64$ ($n = 3$), and $P\bar{v}_{IF}/PET_{IF} = 0.68$ ($n = 3$). The inhalational anesthetics were then discontinued, and intravenous agents were reinstituted, allowing $PET_H$ and $PET_{IF}$ to decrease below 0.50 mm Hg (step 4). Two-lung ventilation was resumed at the end of the surgical procedure (step 5). $PaO_2$ decreased from 441 ± 64 to 252 ± 70 mm Hg when one-lung ventilation was achieved (steps 1–2), and $PaO_2$ increased from 258 ± 72 to 395 ± 65 mm Hg when two-lung ventilation was resumed (steps 4–5). There was no significant change in $PaO_2$ during one-lung ventilation either before, during, or after the administration of H or IF (steps 2–3 and 3–4). The administration of both inhalational anesthetics did not cause a significant decrease in cardiac index ($n$ = 20), $\dot{Q}s/\dot{Q}t$, $P\bar{v}_{O_2}$, or pulmonary artery pressure ($n$ = 10) or dependent lung compliance ($n$ = 20). Our primary conclusion is that H and IF do not further impair arterial oxygenation during one-lung ventilation in intravenously anesthetized patients undergoing thoracotomy. Our respiratory, hemodynamic, and anesthetic depth measurements led us to our second conclusion, by the method of excluding other possible explanatory mechanisms, that these drugs probably did not inhibit hypoxic pulmonary vasoconstriction during one-lung ventilation.*

Key Words: ANESTHESIA—thoracic. ANESTHETIC TECHNIQUES—one-lung ventilation. ANESTHETICS, VOLATILE—halothane, isoflurane. LUNG—atelectasis, blood flow, oxygen, shunting. SURGERY—thoracic. VENTILATION—one-lung.

Hypoxic pulmonary vasoconstriction (HPV) is considered to be an important mechanism by which blood flow is diverted away from atelectatic or hypoxic regions of the lung to its better ventilated normoxic regions. This blood flow diversion minimizes venous admixture and decreases arterial oxygen tension. Numerous studies in animals (1–11,13,14) and one human volunteer study (12) indicate that the inhalational anesthetics halothane (1–12) and isoflurane (5,13,14) inhibit HPV. Extrapolating from these studies, many authors have recommended that inhalational anesthetics be used with caution in situations in which HPV may be operating, for fear they may precipitate arterial hypoxemia (15–18). An example of such a clinical situation is the use of one-lung ventilation (1-LV) to facilitate the performance of thoracic surgery. If inhalational anesthetics significantly inhibit HPV in humans, and all other factors that might influence $PaO_2$ remain relatively constant, then the administration of inhalational anesthetics during one-lung ventilation should decrease $PaO_2$. We tested this hypothesis by measuring $PaO_2$ before, during, and after the administration of halothane and isoflurane to intra-

---

This research was supported by the University of California San Diego, Department of Anesthesia.

Received from the Department of Anesthesia, University of California San Diego, La Jolla, California. Accepted for publication May 15, 1985.

Address correspondence to Dr. Benumof, University of California San Diego, Anesthesia Research Laboratory T-001, La Jolla, California 92093.

© 1985 by the International Anesthesia Research Society

Table 1. Preoperative Demographic Patient Profile

| Inhalational anesthetic | Patient number | Age (yr) | Weight (kg) | Height (cm) | RA ABG (mm Hg) | | PFTS (% of predicted) | | | Surgical procedure | Intravenous anesthetic |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | $Pa_{O_2}$ | $Pa_{CO_2}$ | VC | FRC | MMEF | | |
| Halothane | 1 | 20 | 45 | 129 | 94 | 36 | — | — | — | L subclavian artery resection | M |
| | 2 | 56 | 67 | 178 | 76 | 40 | 81 | 135 | 31 | L wedge resection | K |
| | 3 | 63 | 70 | 183 | 72 | 36 | 110 | 106 | 54 | L upper lobectomy | M |
| | 4 | 42 | 71 | 180 | 100 | 42 | — | — | — | L lung biopsy | M |
| | 5 | 34 | 83 | 180 | 97 | 37 | — | — | — | R upper lobectomy | K |
| | 6 | 59 | 81 | 171 | 64 | 37 | 63 | 156 | 17 | R lung biopsy | K |
| | 7 | 56 | 75 | 125 | 84 | 39 | 75 | 108 | 42 | R upper lobectomy | K |
| | 8 | 66 | 77 | 183 | 65 | 42 | 85 | 134 | 32 | L upper lobectomy | M |
| | 9 | 54 | 70 | 173 | 92 | 34 | 103 | 122 | 20 | L upper lobectomy | M |
| | 10 | 58 | 77 | 165 | 78 | 35 | 101 | 170 | 18 | L upper lobectomy | K |
| Isoflurane | 1 | 59 | 56 | 175 | 57 | 44 | — | — | — | R pleurodesis | K |
| | 2 | 44 | 64 | 103 | 87 | 34 | — | — | — | L esophageal myotomy | K |
| | 3 | 62 | 45 | 170 | 65 | 41 | 62 | 102 | 13 | L decortication | M |
| | 4 | 20 | 50 | 130 | 90 | 36 | — | — | — | L lung biopsy | M |
| | 5 | 58 | 52 | 158 | 86 | 38 | 88 | 111 | 62 | R upper lobectomy | M |
| | 6 | 45 | 40 | 135 | 97 | 40 | — | — | — | L thoracoplasty | K |
| | 7 | 60 | 77 | 107 | 72 | 38 | 98 | 93 | 100 | R wedge resect | K |
| | 8 | 62 | 55 | 165 | 67 | 36 | 59 | 74 | 29 | L pneumonectomy | M |
| | 9 | 64 | 75 | 184 | 71 | 35 | 104 | 111 | 73 | R upper lobectomy | M |
| | 10 | 64 | 56 | 173 | 69 | 37 | 92 | 132 | 35 | R upper lobectomy | K |

Abbreviations: RA, room air; ABG, arterial blood gases; PFTs, pulmonary function tests; VC, vital capacity; FRC, functional residual capacity; MMEF, maximum mid-expiratory flow rate; L, left; R, right; M, methohexital; K, ketamine.

venously anesthetized patients who required lateral thoracotomy and were under stable one-lung ventilation conditions.

## Methods

### Subjects

This study was approved by the University of California San Diego Human Subjects Committee, and all subjects gave their informed consent. The subjects were twenty adult patients who required thoracotomy and one-lung ventilation for various surgical procedures (Table 1). Subjects were alternatively assigned to either a halothane-receiving ($n = 10$) or isoflurane-receiving ($n = 10$) inhalational anesthetic study group. Within these two inhalational anesthetic study groups, subjects were alternatively assigned to either a ketamine-receiving or methohexital-receiving intravenous anesthetic subgroup.

### Monitoring

All patients had radial artery catheters placed for arterial blood pressure (SAP), blood gas, and hemoglobin measurements. Five patients in each inhalational anesthetic study group had central venous catheters placed for central venous pressure and dye dilution cardiac output measurements. The other five patients in each inhalational anesthetic study group had flow-directed pulmonary artery catheters inserted via the right internal jugular vein for pulmonary artery pressure (PAP), mixed venous blood gas, and thermodilution cardiac output measurements. The mean of all blood pressures was electronically determined and recorded on paper (Hewlett–Packard). In all patients the partial pressure (mm Hg) of inhalational anesthetic in end-tidal gas (PET) was measured continuously by mass spectrometry (Chemtron). The partial pressure of inhalational anesthetic in arterial blood (Pa) in five patients in each inhalational anesthetic study group and in mixed venous blood ($P\bar{v}$) in three patients in each inhalational anesthetic subgroup was determined by equilibration tonometry gas chromatography (19) (Hewlett–Packard). Additional monitoring in all patients included esophageal temperature, electrocardiogram, peak and plateau inspiratory airway pressure, and tidal volume measurements. Effective (static) compliance was calculated by dividing tidal volume by plateau airway pressure.

### *Intravenous Anesthesia, Induction, and Maintenance*

Subjects either were unpremedicated, or they received diazepam orally, 10 mg, or morphine intramuscularly, 0.1 mg/kg, 1 hr before entering the operating room. Intravenous anesthesia was induced with divided doses of diazepam, 0.15 mg/kg, fentanyl, 5 μg/kg, and either ketamine, 2 mg/kg, or methohexital, 1 mg/kg. Intravenous anesthesia was maintained with a constant infusion of either ketamine, 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or methohexital, 0.1 $mg \cdot kg^{-1} \cdot min^{-1}$. All subjects were paralyzed with a combination of pancuronium, 0.04 mg/kg, and metocurine, 0.15 mg/kg. Additional doses of pancuronium were administered as needed for muscle relaxation. During intravenous anesthesia, intravenous fluids were administered so that neither systemic arterial, central venous, nor pulmonary artery diastolic pressures varied by more than 10% from preinduction values.

### *Ventilation*

After anesthetic induction, a left-sided double-lumen endotracheal tube (National Catheter Corporation) was inserted, and its proper position was confirmed initially by unilateral airway clamping and chest auscultation maneuvers. After the patient was turned into the lateral decubitus position, correct positioning of the double-lumen endotracheal tube was confirmed by fiberoptic bronchoscopy.

Two-lung ventilation conditions (steps 1 and 5, see experimental sequence section for description of the five steps) consisted of $F_{IO_2}$, 1.0; tidal volume, 12 ml/kg; and respiratory rate adjusted to achieve a value of $Pa_{CO_2}$ between 35 and 40 mm Hg. One-lung ventilation conditions (steps 2–4) were $F_{IO_2}$, 1.0; tidal volume, 10 ml/kg; and respiratory rate adjusted so that $Pa_{CO_2}$ was between 35 and 40 mm Hg.

### *Inhalational Anesthesia*

Inhalational anesthetics were administered (step 3) with a Drager flow-over vaporizer via a circle system with a high fresh oxygen flow and initial over-pressure in order to reach the desired end-tidal inhalational anesthetic concentration (greater than 1 MAC) within 5 min. This end-tidal inhalational anesthetic concentration was then held nearly constant for more than 15 min. Arterial blood (from five patients in each inhalational anesthetic group) and mixed venous blood (from three patients in each inhalational anesthetic group) was drawn for gas chromatographic determination of inhalational anesthetic concentration by equilibration tonometry at the end of the inhalational anesthetic administration period. Inhalational anesthetics were then discontinued and end-tidal concentrations allowed to decrease to less than 0.50 mm Hg during one-lung ventilation (step 4). During inhalational anesthesia, intravenous fluids were administered so that neither systemic arterial, central venous, nor pulmonary artery diastolic pressures varied by more than 15% from preinduction values.

### *Experimental Sequence*

Our experimental sequence consisted of five steps. Step 1 was two-lung ventilation during intravenous anesthesia. Final measurements made during step 1 were obtained after the pleura was opened. Step 2 was one-lung ventilation during intravenous anesthesia. One-lung ventilation conditions were initiated after the pleura was incised by opening one side of the double-lumen tube to atmosphere, and they were confirmed by visual observation of lung collapse and mediastinal movement. In addition, in order to demonstrate achievement of stable one-lung ventilation conditions, serial arterial blood gas measurements ($Pa_{O_2}$) were obtained during step 2 until two consecutive $Pa_{O_2}$ determinations were near equal (±32 mm Hg) and separated by at least 5 min. Step 3 was to discontinue intravenous anesthetics (which ended step 2) and to administer inhalational anesthesia (as described above) during one-lung ventilation. Step 4 was to discontinue inhalational anesthesia (which ended step 3) and to readminister intravenous anesthesia (as before) during one-lung ventilation. Steps 2, 3, and 4 were always completed before any pulmonary vessels were ligated, and all measurements were made when the surgeons were not compressing the nondependent lung, blood loss was minimal, and the patients were hemodynamically stable. Step 5 was two-lung ventilation during intravenous anesthesia. We returned to two-lung ventilation conditions under intravenous anesthesia near the end of the surgical procedure before the pleura was closed. The experimental sequence and approximate time for each step is summarized below.

Step 1) Two-lung ventilation, intravenous anesthesia (20–30 min).
Step 2) One-lung ventilation, intravenous anesthesia (20–40 min).
Step 3) One-lung ventilation, inhalational anesthesia (15–30 min).

Table 2. Average Values (± SD) Obtained at Each Experimental Step in Both Study Groups for Patients ($n$ = 10)

| Function | Variable | Anesthetic | Experimental Step | | | | |
|---|---|---|---|---|---|---|---|
| | | | 1 (2-LV, IV) | 2 (1-LV, IV) | 3 (1-LV, IH) | 4 (1-LV, IV) | 5 (2-LV, IV) |
| Ventilation and gas exchange | $Pa_{O_2}$ (mm Hg) | HAL | 437 ± 87 | 224 ± 108[b] | 234 ± 102 | 237 ± 105 | 388 ± 94[b] |
| | | ISO | 445 ± 75 | 283 ± 116[b] | 278 ± 122 | 281 ± 130 | 414 ± 85[b] |
| | $Pa_{CO_2}$ (mm Hg) | HAL | 36 ± 5 | 37 ± 5 | 35 ± 4 | 35 ± 4 | 36 ± 4 |
| | | ISO | 38 ± 6 | 38 ± 5 | 37 ± 6 | 36 ± 5 | 36 ± 6 |
| | $\dot{Q}s/\dot{Q}t$ (%)[a] | HAL | 20 ± 4 | 31 ± 8[b] | 29 ± 10 | 28 ± 9 | 22 ± 7[b] |
| | | ISO | 22 ± 8 | 33 ± 13[b] | 34 ± 12 | 30 ± 12 | 24 ± 9[b] |
| | Pao peak/plateau (cm $H_2O$) | HAL | 23/20 ± 4/5 | 29/24 ± 3/5[b] | 29/25 ± 3/6 | 29/25 ± 3/6 | 26/21 ± 4/5[b] |
| | | ISO | 26/22 ± 5/4 | 31/27 ± 2/2[b] | 31/27 ± 2/2 | 31/27 ± 2/2 | 26/22 ± 3/3[b] |
| | $C_{STA}$ (ml/cm $H_2O$) | HAL | 45 ± 10 | 31 ± 8 | 32 ± 9 | 32 ± 9 | 43 ± 10 |
| | | ISO | 42 ± 11 | 31 ± 8 | 30 ± 7 | 30 ± 7 | 40 ± 10 |
| Hemodynamics | SAP (mm Hg) | HAL | 92 ± 11 | 92 ± 14 | 71 ± 12[b] | 88 ± 11[b] | 86 ± 8 |
| | | ISO | 99 ± 11 | 95 ± 10 | 78 ± 12[b] | 92 ± 6[b] | 93 ± 8 |
| | CI ($L \cdot min^{-1} \cdot m^{-2}$) | HAL | — | 3.1 ± 0.6 | 2.9 ± 0.9 | 3.1 ± 0.6 | — |
| | | ISO | — | 3.1 ± 0.5 | 2.8 ± 0.5 | 2.9 ± 0.5 | — |
| | $P\bar{v}_{O_2}$[a] (mm Hg) | HAL | 51 ± 10 | 43 ± 1 | 42 ± 5 | 43 ± 3 | 48 ± 6 |
| | | ISO | 54 ± 6 | 49 ± 5 | 50 ± 6 | 44 ± 3 | 50 ± 4 |
| | $C(a-\bar{v})_{O_2}$ (vol %)[a] | HAL | 3.7 ± 1.2 | 3.9 ± 0.5 | 4.4 ± 1.2 | 4.2 ± 0.7 | 3.7 ± 0.7 |
| | | ISO | 3.2 ± 0.8 | 3.3 ± 0.8 | 3.1 ± 0.4 | 4.2 ± 0.7 | 3.4 ± 0.5 |
| | PAP (mm Hg)[a] | HAL | 17 ± 2 | 19 ± 2 | 18 ± 3 | 19 ± 3 | 17 ± 2 |
| | | ISO | 13 ± 1 | 14 ± 2 | 13 ± 2 | 14 ± 3 | 13 ± 2 |

Abbreviations: 2-LV, two-lung ventilation; 1-LV, one-lung ventilation; IV, intravenous anesthesia; IH, inhalation anesthesia; HAL, halothane; ISO, isoflurane; SAP, systemic arterial pressure (mean); PAP, pulmonary artery pressure (mean); Pao, airway pressure.

[a] $n = 5$ patients with pulmonary artery catheters.

[b] $P < 0.05$ compared to previous experimental step.

Step 4) One-lung ventilation, intravenous anesthesia (30–40 min).

Step 5) Two-lung ventilation, intravenous anesthesia (20–30 min).

### *Calculations*

The following formulas were used to calculate venous admixture in the five patients in each inhalational anesthetic study group with pulmonary artery catheters. Alveolar oxygen tension:

$$P_{AO_2} = F_{IO_2} \times (P_B - P_{H_2O}) - Pa_{CO_2}.$$

Oxygen content:

$$C = (1.34 \times Hgb \times \%\ Sat) + (0.003 \times P_{O_2}).$$

Venous admixture:

$$\dot{Q}s/\dot{Q}t = (Cc'_{O_2} - Ca_{O_2})/(Cc'_{O_2} - C\bar{v}_{O_2}).$$

Hemoglobin saturation was calculated from $P_{O_2}$ corrected for $P_{CO_2}$, pH, and temperature, using the method of Kelman (20).

### *Statistics*

All results were analyzed by *F*-test and Student's paired *t*-analysis, with $P < 0.05$ considered significant. Results are expressed as individual patient data and as mean ± SD for each inhalational anesthetic group.

## Results

Average values that characterized ventilation and gas exchange, and hemodynamics at each experimental step in each inhalation anesthetic group are presented in Table 2 and Figures 1 and 2. Individual patient end-tidal, arterial blood, and mixed venous blood inhalational anesthetic partial pressures are presented in Table 3. There was no significant difference between results obtained in the ketamine vs methohexital intravenous anesthetic subgroups; thus they are presented together in Tables 2 and 3, Figures 1 and 2, and in the text.

### *Respiration*

Initiation of one-lung ventilation caused a significant decrease in $Pa_{O_2}$. Figure 1 shows serial $Pa_{O_2}$ determinations in individual patients obtained during the transition between two-lung and one-lung ventilation during intravenous anesthesia (steps 1–2). The $Pa_{O_2}$ represented by the triangles in Figure 1 was taken to represent the $Pa_{O_2}$ during stable one-lung ventilation

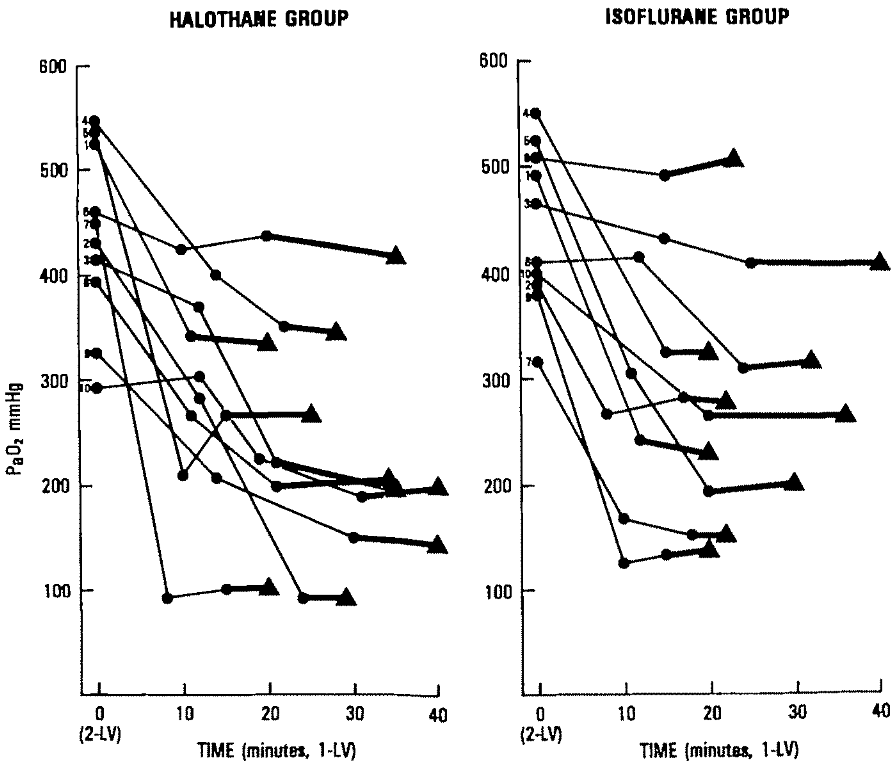


Figure 1. Changing from two-lung ventilation (2-LV) to one-lung ventilation (1-LV) causes a decrease in $PaO_2$ with time. Halothane and isoflurane groups refer to patients that subsequently receive these drugs. In all patients, two successive $PaO_2$ determinations that were ± 32 mm Hg of each other and separated by at least 5 min indicated stability of the 1-LV condition (heavy line segment); the $PaO_2$ that was taken to represent the 1-LV condition is indicated by the large triangles and occurred between 20 and 37 min after induction of 1-LV. Individual patients are identified by small numbers to the left of the final 2-LV $PaO_2$ value and are the same identification numbers as in Table 1.

conditions under intravenous anesthesia (step 2). The mean ± SD one-lung ventilation time represented by the triangles for all patients was 27 ± 6 min with a range of 20–37 min. The mean ± SD difference in time between the $PaO_2$ represented by the triangles and the preceding $PaO_2$ for all patients was 8 ± 4 min with a range of 5–20 min. The mean ± SD difference in $PaO_2$ between the $PaO_2$ represented by the triangles and the preceding $PaO_2$ for all patients was 13 ± 10 mm Hg with a range of 0–32 mm Hg.

There was no significant change in $PaCO_2$ throughout the entire 5-step experimental sequence (Table 2). There was a significant increase in both peak and plateau inspiratory airway pressures with the initiation of one-lung ventilation, but they remained constant during one-lung ventilation (steps 2–4).

### *Anesthetic Depth*

Table 3 shows the partial pressure of inhalational anesthetic in end-tidal gas ($PET_H$, $PET_{IF}$) in all patients, arterial blood ($Pa_H$ ($n$ = 5), $Pa_{IF}$ ($n$ = 5), and mixed venous blood ($P\bar{v}_H$ ($n$ = 3), $P\bar{v}_{IF}$ ($n$ = 3)). The average end-tidal inhalational anesthetic levels achieved and maintained during step 3 were equivalent to 1.45 MAC for halothane and 1.15 MAC for isoflurane. The arterial blood inhalational anesthetic levels obtained in five patients in both the halothane and isoflurane inhalation anesthetic study groups averaged 82% and 75% of the end-tidal levels, respectively. These arterial blood levels are equivalent to an average of 1.20 MAC for halothane and 0.88 MAC for isoflurane. Mixed venous inhalational anesthetic blood levels obtained in the three patients in each study group at the end of step 3 averaged 64% and 68% of the end-tidal levels for halothane and isoflurane, respectively. These mixed venous blood levels corresponded to an average of 0.95 and 0.82 MAC for halothane and isoflurane, respectively.

### *Hemodynamics*

There was a significant decrease in systemic arterial blood pressure with the administration of either inhalational anesthetics (Table 2). There was a small but nonsignificant decrease in both cardiac index and pulmonary artery pressure with the administration of inhalational anesthetics in both groups (Table 2). There was no significant change in arteriovenous oxygen content difference or mixed venous oxygen tension associated with the administration of inhalational anesthetics (Table 2).

### *Arterial Oxygenation*

Figure 2 and Table 2 show average $PaO_2$ results, and Figure 2 also shows individual patient $PaO_2$ results

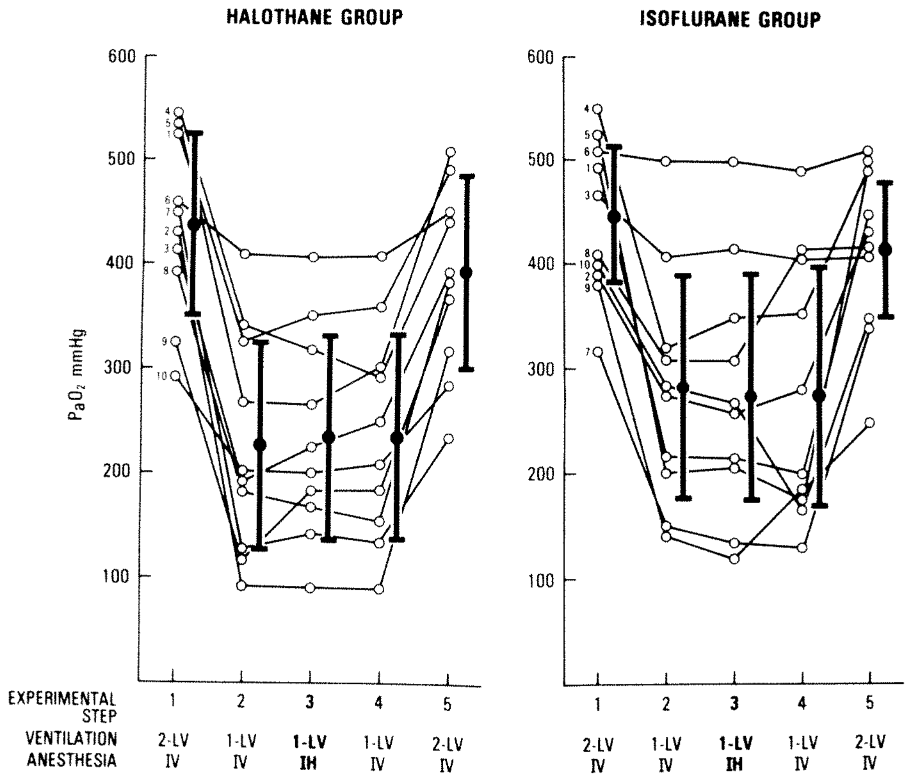


Figure 2. Changes in $Pa_{O_2}$ throughout the entire experimental sequence (experimental steps 1–5) Abbreviations: 2-LV, two-lung ventilation; 1-LV, one-lung ventilation; IV, intravenous anesthesia; IH, inhalational anesthesia. The 2-LV and first 1-LV $Pa_{O_2}$ values are the same as the first and last (triangles) $Pa_{O_2}$ values in Figure 1. Patients are divided according to the inhalational anesthetic drug they received (halothane or isoflurane). Open circles are individual patient data and closed circles are mean ± SD for each group (same values as in top row of Table 2).

obtained at each experimental step in both inhalational anesthetic study groups. There was no significant decrease in the $Pa_{O_2}$ obtained during administration of either halothane or isoflurane (end of step 3) compared to that obtained under intravenous anesthesia during one-lung ventilation (steps 2 and 4). Table 2 also shows the average venous admixture calculated for the five patients in each study group with pulmonary artery catheters. There was no significant change in venous admixture associated with the administration of halothane or isoflurane during one-lung ventilation.

## Discussion

We found that halothane and isoflurane do not further impair arterial oxygenation during one-lung ventilation in intravenously anesthetized patients. Consideration should be given to several key issues, namely, the stability of the one-lung ventilation conditions, the presence of HPV in the atelectatic lung, and the achievement of an adequate atelectatic lung concentration of inhalational anesthetic.

Crucial to the interpretation of our findings that halothane and isoflurane did not impair arterial oxygenation during one-lung ventilation is evidence that we achieved stable one-lung ventilation conditions in each patient. It is possible that not enough time was allowed for complete stabilization of one-lung ventilation during step 2; decreases in blood flow to canine atelectatic lung recently were found not to be maximal until 60 min (21). However, there are three arguments that support the contention that one-lung ventilation conditions had stabilized by the end of step 2. First, and most important, serial $Pa_{O_2}$ determinations (Fig. 1) demonstrated two near-equal $Pa_{O_2}$ values separated by at least 5 min in each patient. Second, previous studies during one-lung ventilation in humans suggest that $Pa_{O_2}$ and $\dot{Q}s/\dot{Q}t$ stabilizes within 15–20 min (22,23), and we maintained one-lung ventilation under intravenous anesthesia (step 2) for at least 20 min in every patient. Third, there was no significant difference between $Pa_{O_2}$ during step 2 compared to step 4. $Pa_{O_2}$ measurements during step 4 were obtained at least 60 min after the initiation of one-lung ventilation.

Our $\dot{Q}s/\dot{Q}t$ calculations in the patients that had pulmonary artery catheters and the $Pa_{O_2}$ measurements in all patients indicate that blood flow to the nondependent lung was markedly decreased when it was nonventilated. Average $\dot{Q}s/\dot{Q}t$ during two-lung ventilation was approximately 20%. If this shunt were shared equally by both lungs, then the dependent lung would be responsible for about a 10% shunt. During one-lung ventilation average total shunt was approximately 30%. Assuming that all of the 10% in-

Table 3. Individual Patient Anesthetic Depth Level at the End of Experimental Step 3[a]

| Anesthetic | Patient number | $P_{ET}$ (mm Hg) | Pa (mm Hg) | $P_{\bar{v}}$ (mm Hg) | $\frac{Pa}{P_{ET}}$ | $\frac{P_{\bar{v}}}{P_{ET}}$ | $P_{ET}$ (MAC) | Pa (MAC) | $P_{\bar{v}}$ (MAC) |
|---|---|---|---|---|---|---|---|---|---|
| Halothane | 1 | 7.86 | — | — | — | — | — | — | — |
| | 2 | 6.72 | — | — | — | — | — | — | — |
| | 3 | 7.34 | — | — | — | — | — | — | — |
| | 4 | 7.02 | — | — | — | — | — | — | — |
| | 5 | 7.55 | — | — | — | — | — | — | — |
| | 6 | 7.55 | 4.53 | — | 0.60 | — | 1.33 | 0.80 | — |
| | 7 | 8.31 | 7.55 | — | 0.91 | — | 1.47 | 1.33 | — |
| | 8 | 8.46 | 6.19 | 4.91 | 0.73 | 0.58 | 1.49 | 1.09 | 0.87 |
| | 9 | 8.38 | 7.93 | 4.76 | 0.95 | 0.57 | 1.48 | 1.40 | 0.84 |
| | 10 | 8.15 | 7.78 | 6.42 | 0.93 | 0.77 | 1.48 | 1.37 | 1.13 |
| | Mean | 7.70 | 6.79 | 5.36 | 0.82 | 0.64 | 1.45 | 1.20 | 0.95 |
| | ± SD | ±0.61 | ±1.44 | ±0.91 | ±0.15 | ±0.11 | ±0.07 | ±0.25 | ±0.16 |
| Isoflurane | 1 | 9.89 | — | — | — | — | — | — | — |
| | 2 | 8.76 | 5.06 | — | 0.58 | — | 1.01 | 0.58 | — |
| | 3 | 10.04 | — | — | — | — | — | — | — |
| | 4 | 10.95 | — | — | — | — | — | — | — |
| | 5 | 10.80 | — | — | — | — | — | — | — |
| | 6 | 7.55 | — | — | — | — | — | — | — |
| | 7 | 9.82 | 4.76 | — | 0.49 | — | 1.13 | 0.55 | — |
| | 8 | 10.42 | 8.38 | 7.55 | 0.80 | 0.73 | 1.20 | 0.97 | 0.87 |
| | 9 | 10.04 | 9.29 | 7.02 | 0.93 | 0.70 | 1.16 | 1.07 | 0.81 |
| | 10 | 10.95 | 10.65 | 6.72 | 0.97 | 0.61 | 1.26 | 1.23 | 0.77 |
| | Mean | 9.89 | 7.63 | 7.10 | 0.75 | 0.68 | 1.15 | 0.88 | 0.82 |
| | ± SD | ±1.08 | ±2.61 | ±0.42 | ±0.21 | ±0.06 | ±0.09 | ±0.30 | ±0.05 |

[a] Abbreviations: $P_{ET}$, partial pressure end tidal; Pa, partial pressure arterial; $P_{\bar{v}}$, partial pressure mixed venous; MAC, minimum alveolar concentration.

crease in shunt (20–30%) occurred in the lung that was not being ventilated, the nonventilated nondependent lung would have been responsible for a 20% shunt (and 20% of the total pulmonary blood flow).

There are several possible reasons why blood flow to the nondependent lung was markedly decreased when it was nonventilated. First, although surgical interference ordinarily may be a cause of reduced nondependent nonventilated lung blood flow, we made our measurements when the lung was not being manipulated. Second, extensive preoperative disease in the nondependent lung may markedly decrease nondependent lung blood flow. The induction of one-lung ventilation in a markedly diseased lung may not decrease $PaO_2$ because the lung has only a small amount of blood flow to begin with. This may have been the case in three of our patients (numbers 3 and 6 in the group given isoflurane, and number 6 in the group given halothane) who had extensive preoperative consolidation of the operated (collapsed) lung, and minimal changes in $PaO_2$ with one-lung ventilation. However, all the rest of our subjects had either small, well localized tumors or no pulmonary pathology and had significant decreases in $PaO_2$ with one-lung ventilation. The range of $PaO_2$ responses to one-lung ventilation we observed is consistent with previous findings (12,18,22,23). Third, blood flow to the nondependent lung is reduced by the force of gravity. Thus when the right lung is nondependent, it should receive 45% of total blood flow (as opposed to 55% of total flow in the upright and supine positions); and, when the left lung is nondependent, it should receive 35% of total blood flow (as opposed to 45% of total flow in the upright and supine position) (24,25). Consequently, hydrostatic factors alone cannot explain the magnitude of decreased blood flow to the nondependent lung when it was nonventilated. Finally, blood flow to the nondependent lung can be decreased by HPV. Since the other three mechanisms were either absent (the first one), present in only a small number of patients (the second one), or made only a relatively minor contribution (the third one), the HPV mechanism was probably the major one and, therefore, requires further comment.

The following logic supports the contention that blood flow to the nondependent lung was acutely reduced by HPV when it was nonventilated. If the nondependent lung, when ventilated, received an average of 40% of the total pulmonary blood flow (see above), and when nonventilated received 20% of the total pulmonary blood flow (see above), nondependent lung blood flow must have decreased by an average of 50% during one-lung ventilation (40–20% of total pulmonary blood flow). If the initial two-lung ventilation shunt of 20% was distributed 15% to the dependent lung (as it might well be due to compression of the dependent lung) and 5% to the nondependent lung, then similar reasoning would result in an average decrease in nondependent lung blood flow of 62%. These numbers (50–62%) are very close to the amount of blood flow reduction expected of single lung HPV (26). The contention that blood flow to the nondependent lung was decreased by HPV is also consistent with previous studies showing that the major mechanism of decreased blood flow to atelectatic lung is by HPV (as opposed to mechanical factors) (1,27,28). The contention is also consistent with previous studies showing no significant effect of intravenous anesthetic drugs on HPV (2,3,10,13,18,29,30). In addition, our $PaO_2$ values during two-lung ventilation were also consistent with the contention that intravenous anesthesia did not significantly impair arterial oxygenation (or HPV).

The nonventilated lung was probably exposed to a clinically significant depth of inhalational anesthetics during step 3 for several reasons. First, we demonstrated clinically relevant end-tidal levels in all patients, arterial blood levels in 50% of the patients, and venous blood levels in 30% of the patients. The nonventilated lung tissue level of inhalational anesthetic is most closely approximated by the mixed venous blood level, although the arterial (bronchial) blood level has increased importance under these circumstances. The time constant ($\tau$) for lung tissue equilibration with mixed venous blood for halothane is 0.7 min [$\tau$ = tissue capacity/tissue blood flow = (volume of tissue) × (tissue – blood partition coefficient)/tissue blood flow = 0.5 L × 2.0/1.5 L = 0.7 min] (31,32). Second, our measurements were made at a time when the surgeons were not pressing or retracting the atelectatic lung, so that the atelactatic lung should have been evenly perfused (although with a reduced perfusion). Third, it is probable that the mixed venous blood is more important than the tissue level of inhalational anesthetics because the main site of HPV is in the pulmonary arterioles. Thus given the duration of our inhalational anesthetic administration at the reported constant end-tidal levels, the arterial and mixed venous blood levels, and that the atelectatic lung was most likely well and evenly perfused, we are confident that we achieved clinically significant nonventilated lung inhalational anesthetic levels.

One possible interpretation of our findings that $PaO_2$ did not decrease with the administration of inhalational anesthetics during one-lung ventilation is that halothane and isoflurane inhibited HPV in the nonventilated lung, but that this negative effect on $PaO_2$ was offset by some other process tending to increase arterial oxygenation. Possible offsetting processes include mechanical (surgical) compression of the vessels in the collapsed lung, an increase in $P\bar{v}_{O_2}$, a decrease in PAP, and an improvement in ventilation/perfusion relationships in the ventilated lung. Each of these offsetting processes are unlikely occurrences in our study. First, although mechanical compression of vessels in the nonventilated lung would be expected to redistribute blood to the ventilated lung and thus increase $PaO_2$, we had the cooperation of our surgical colleagues to ensure that no manipulation, retraction, or clamping of either lung occurred during steps 1–4. Step 5 occurred near the end of the surgical procedure after any pulmonary surgery (usually lobectomy) had been completed. Second, an increase in cardiac output or a decrease in oxygen consumption would be expected to increase $P\bar{v}_{O_2}$ and thus increase $PaO_2$ independent of changes in $\dot{Q}s/\dot{Q}t$. Not only was there no significant change in cardiac output during step 3 but, in the five patients with pulmonary artery catheter monitoring, there was no significant change in $P\bar{v}_{O_2}$ or calculated $C(a\text{-}\bar{v})O_2$. Third, a decrease in PAP would be expected to decrease flow to the nondependent nonventilated lung. In the five patients in each group with pulmonary artery catheter monitoring there was no change in PAP, suggesting that no significant redistribution of flow due to a change in PAP occurred. These PAP findings are consistent with previous reports in humans (33,34). Fourth, the bronchodilating effects of inhalational agents might have improved ventilation/perfusion matching in the ventilated lung so as to offset any adverse effects of the inhalational anesthetics on $PaO_2$ or $\dot{Q}s/\dot{Q}t$. There was no change in dynamic or static lung compliance (as indicated by the constant peak and plateau inspiratory airway pressures) indicating that significant bronchodilation did not occur.

If all other factors that affect $PaO_2$ are constant, inhibition of regional HPV should decrease $PaO_2$. Because none of the above offsetting mechanisms can explain our primary finding of no change in $PaO_2$ with administration of inhalational anesthesia during one-lung ventilation, we conclude secondarily that halothane and isoflurane do not significantly inhibit HPV at approximately 1-MAC doses in humans. Differences between our study and the large number of previous animal studies concerning the effects of inhalational anesthetics on HPV, which arrived at an opposite conclusion from ours, include use of different species (35–37) and different methodology (such as use of pump perfused preparations); both of these considerations may involve altered neural, chemical, and humoral influences (38,39). Because both halothane and isoflurane have a number of desirable properties (allow use of a high $F_{I_{O_2}}$, are rapidly elminated, have a salutary effect on bronchomotor tone) in addition to not adversely affecting arterial oxygenation during one-lung ventilation, we think they are desirable anesthetics to use for thoracic surgery.

## References

1. Bjertnaes LJ, Mundal R, Hauge A, Nicolaysen A. Vascular resistance in atelectatic lungs: effect of inhalation anesthetics. Acta Anaesthesiol Scand 1980;24:109–18.
2. Bredesen J, Bjertnaes L, Hauge A. Effects of anesthetics on the pulmonary vasoconstrictor response to acute alveolar hypoxia. Microvasc Res 1975;10:236.
3. Bjertnaes LJ. Hypoxia-induced vasoconstriction in isolated perfused lungs exposed to injectable or inhalation anesthetics. Acta Anaesthesiol Scand 1977;21:133–47.
4. Bjertnaes LJ, Hauge A, Torgrinsen T. The pulmonary vasoconstrictor response to hypoxia. The hypoxia-sensitive site studied with a volatile inhibitor. Acta Physiol Scand 1980;109:447–62.
5. Marshall C, Lindren L, Marshall BE. The effect of inhalation anesthetics on HPV. Anesthesiology 1983;59:A527.
6. Sykes MK, Davies DM, Chakrabarti MK, Loh L. The effects of halothane, trichlorethylene and ether on the hypoxic pressor response and pulmonary vascular resistance in the isolated, perfused lung. Br J Anaesth 1973;45:655–63.
7. Gibbs JM, Sykes MK, Tait AR. Effects of halothane and hydrogen ion concentration on the alteration of pulmonary vascular resistance induced by graded alveolar hypoxia in the isolated perfused cat lung. Anaesth Intensive Care 1974;2:231–9.
8. Loh L, Sykes MK, Chakrabarti MK. The effects of halothane and ether on the pulmonary circulation in the isolated perfused cat lung. Br J Anaesth 1977;49:309–14.
9. Buckley MJ, McLaughlin JS, Fort L III, Saigusa M, Morrow DH. Effects of anesthetic agents on pulmonary vascular resistance during hypoxia. Surg Forum 1964;15:183–4.
10. Lumb TD, Silvay G, Weinreich AI, Shiang W. A comparison of the effects of continuous ketamine infusion and halothane on oxygenation during one lung anesthesia in dogs. Can Anaesth Soc J 1979;26:394–401.
11. Hall SM, Chapleau M, Cairo J, Levitzky MG. The effect of high frequency ventilation on halothane ablation of hypoxic pulmonary vasoconstriction. Fed Proc 1983;42:595.
12. Bjertnaes LJ. Hypoxia induced pulmonary vasoconstriction in man: inhibition due to diethyl ether and halothane anesthesia. Acta Anaesthesiol Scand 1978;22:570–88.
13. Benumof JL, Wahrenbrock EA. Local effects of anesthesia on regional hypoxic pulmonary vasoconstriction. Anesthesiology 1975;43:525–32.
14. Mathers J, Benumof JL, Wahrenbrock EA. General anesthetics and regional hypoxic pulmonary vasoconstriction. Anesthesiology 1977;46:111–14.
15. Pavlin EG. Respiratory pharmacology of inhaled anesthetic agents. In: Miller RD, ed. Anesthesia. New York: Churchill-Livingston, 1981:349–82.
16. Silvay G, Weinreich AI, Eisenkraft JB. Anesthesia for pulmonary surgery, thoracic anesthesia. In: Kaplan JA, ed. Thoracic anesthesia. New York: Churchill-Livingston, 1983:347–87.
17. Bergman NA. Pulmonary circulation in relation to anaesthesia and pulmonary edema. In: Gray TC, Nunn JF, Utting JE, eds. General anaesthesia. London: Butterworths, 1980:477–91.
18. Bjertnaes LJ. Intravenous versus inhalation anesthesia—pulmonary effects. Acta Anaesthesiol Scand [Suppl] 1982;75:18–24.
19. Dueck R, Rathburn M, Wagner PD. Chromatographic analysis of multiple tracer inert gases in the presence of anesthetic gases. Anesthesiology 1978;49:31–6.
20. Kelman GR. Digital computer subroutine for the conversion of oxygen tension into saturation. J Appl Physiol 1966;21:1375–6.
21. Glasser SA, Domino KB, Lindgren L, Parcella P, Marshall C, Marshall BE. Pulmonary blood pressure and flow during atelectasis in the dog. Anesthesiology 58:225–31, 1983.
22. Torda TA, McCulloch CM, O'Brien HD, Wright JS, Horton DA. Pulmonary venous admixture during one-lung anaesthesia. Anaesthesia 1974;29:272–9.
23. Petola K. Central haemodynamics and oxygenation during thoracic anaesthesia. Acta Anaesthesiol Scand [Suppl 77] 1983;27:1–51.
24. Wulff KE, Aulin I. The regional lung function in the lateral decubitus position during anesthesia and operation. Acta Anaesth Scand 1972;16:195–205.
25. Rehder K, Wenthe FM, Sessler AD. Function of each lung during mechanical ventilation with ZEEP and with PEEP in man anesthetized with thiopental-meperidine. Anesthesiology 1973;39:597–606.
26. Marshall BE, Marshall C. Continuity of response to hypoxic pulmonary vasoconstriction. J Appl Physiol 1980;49:189–96.
27. Benumof JL. Mechanism of decreased blood flow to atelectatic lung. J Appl Physiol 1978;46:1047–8.
28. Pirlo AF, Benumof JL, Trousdale FR. Atelectatic lobe blood flow: open versus closed chest, positive pressure versus spontaneous ventilation. J Appl Physiol 1981;50:1022–6.
29. Gibbs JM, Johnson H. Lack of effect of morphine and buprenorphine on hypoxic pulmonary vasoconstriction in the isolated perfused cat lung and the perfused lobe of the dog lung. Br J Anaesth 1978;50:1197–201.
30. Weinreich AI, Silvay G, Lumb PB. Continuous ketamine infusion for one-lung anesthesia. Can Anaesth Soc J 1980;27:485–90.
31. Steward A, Allott PR, Cowles AL, Mapleson WW. Solubility coefficients for inhaled anaesthetics for water, oil and biological media. Br J Anaesth 1973;45:282–93.
32. Larson CP Jr, Eger EI II, Severinghaus JW. Solubility coefficients of inhaled anesthetics in biological media. Anesthesiology 1962;23:349–55.
33. Price HL, Cooperman LH, Warden JC, Morris JJ, Smith TC. Pulmonary hemodynamics during general anesthesia in man. Anesthesiology 1967;30:629–36.
34. Stoelting RK, Reis RR, Longnecker DE. Hemodynamic responses to nitrousoxide-halothane and halothane in patients with valvular heart disease. Anesthesiology 1972;37:430–5.
35. Grover RF, Vogel JHK, Averill KH, Blount SG. Pulmonary hypertension. Individual and species variability relative to vascular reactivity. Am Heart J 1963;66:1–3.
36. Tucker A, McMurtry IF, Alexander AF, Reeves JT, Grover RF. Lung mast cell density and distribution in chronically hypoxic animals. J Appl Physiol 1977;42:174–8.
37. Tucker A, McMurtry IF, Reeves JT, Alexander AF, Will DH, Grover RF. Lung vascular smooth muscle as a determinant of pulmonary hypertension at high altitudes. Am J Physiol 1975;28:762–7.
38. Sykes MK, Gibbs JM, Loh L, Marin JDL, Obdrzalek J, Arnot RN. Preservation of the pulmonary vasoconstrictor response to alveolar hypoxia during the administration of halothane to dogs. Br J Anaesth 1978;50:1185–96.
39. Allison PR, Daly I deB, Waaler BJ. Bronchial circulation and pulmonary vasomotor nerve responses in isolated perfused lungs. J Physiol 1961;157:462.

ANESTH ANALG
1985;64:955–63

# Comparison of the Requirements for Hepatic Injury with Halothane and Enflurane in Rats

Richard C. Lind, MS, A. Jay Gandolfi, PhD, I. Glenn Sipes, PhD, and Burnell R. Brown, JR, MD, PhD

LIND RC, GANDOLFI AJ, SIPES IG, BROWN BR JR. Comparison of requirements for hepatic injury with halothane and enflurane in rats. Anesth Analg 1985;64:955–63.

*A rat model of enflurane-associated hepatotoxicity was compared with the halothane–hypoxia (HH) model (adult male rats, phenobarbital induction, 1% halothane, 14% $O_2$, for 2 hr). The enflurane-hypoxia heating (EHH) model involved exposing phenobarbital-pretreated male adult rats to 1.5–1.8% enflurane at 10% $O_2$ for 2 hr with external heating to help maintain body temperature. Exposure to either anesthetic without temperature support led to a decrease in body temperature of 7–9°C, while heating the animals during anesthesia resulted in only a 0.5–2°C decrease. Reducing the oxygen tension to 10% $O_2$ combined with heating the animals during exposure produced significant decreases in the oxidative metabolism of both halothane and enflurane as compared to exposures of 14% $O_2$. The same conditions also caused a significant increase in the reductive metabolism of halothane, indicating that a severe hepatic hypoxia or anoxia occurs during anesthesia at 10% $O_2$ with external heating. The time course of lesion development in the HH model paralleled results obtained with an oral dose of $CCl_4$: gradual progression of necrosis up to 24 hr. EHH resulted in a classic hypoxic/anoxic injury with elevated serum glutamate pyruvate transaminase values and a watery vacuolization of centrilobular hepatocytes immediately after exposure. The HH model required phenobarbital pretreatment of the rats for expression of hepatic injury; EHH did not. Heating of the animals during anesthesia exposure was necessary for enflurane-induced hepatotoxicity but had little effect on the HH model. Exposure to 5% $O_2$ without anesthetic mimicked EHH in both requirements for and type of hepatic injury. Thus the HH model appears to act via a bioactivation/chemotoxic mechanism, whereas models of anesthetic-induced hepatotoxicity that require very low oxygen tensions and heating of the animals during exposure result from a severe hypoxia/anoxia of the liver.*

Key Words: ANESTHETICS, VOLATILE—enflurane, halothane. LIVER—hepatotoxicity. HYPOXIA—hepatotoxicity.

A unifying mechanism of anesthetic-induced hepatotoxicity has recently been promoted based on hypoxic/anoxic processes (1,2). Extensive centrilobular necrosis was produced in phenobarbital (PB) pretreated male rats by exposure to halothane, enflurane, isoflurane, thiopental, or fentanyl even at subanesthetic concentrations. The exposures were carried out at 10% $O_2$ for 2 hr with warming of the animals to maintain normothermia. It was concluded from these studies that all anesthetics produce hepatic injury via a hypoxic/anoxic mechanism. A previously developed animal model of halothane-associated liver injury, halothane-hypoxia (HH), involves exposing PB-treated male rats to 1% halothane at 14% $O_2$ for 2 hr (3,4). The ability of this animal model to produce hepatic necrosis has been attributed to a chemotoxic mechanism involving binding of reactive metabolic intermediates to subcellular macromolecules (4,5). This study compares the requirements for production of hepatotoxicity and the resultant hepatic lesions produced in the HH model and a model of enflurane-induced hepatotoxicity in rats.

Enflurane was chosen as an agent capable of producing a purely hypoxic/anoxic hepatic injury because it has been shown that enflurane produces neither reactive metabolic intermediates in vivo (5) nor hepatotoxicity under exposure conditions identical to the HH model (6). For these experiments an enflurane–hypoxia heating (EHH) hepatotoxicity model was used in which PB-pretreated male rats were exposed to 1.5–1.8% enflurane at 10% $O_2$ for 2 hr with external heating to help maintain body temperature (2).

In this study the metabolism of halothane and en-

---

Supported by NIH Grant AM 16715.

Received from the Department of Anesthesiology, University of Arizona Health Sciences Center, Tucson, Arizona. Accepted for publication May 15, 1985.

Address correspondence to Mr. Lind, Department of Anesthesiology, University of Arizona Health Sciences Center, Tucson, AZ 85724.

© 1985 by the International Anesthesia Research Society

Table 1. Serum Fluoride Concentrations Immediately after Exposure to Enflurane[a] With or Without External Heating to Help Maintain Normothermia

| Oxygen concentration (% $O_2$) | External heating[b] | Serum fluoride[c] (μM) | *n* |
|---|---|---|---|
| 14 | – | 9.5 ± 1.4 | 4 |
| 14 | + | 13.5 ± 1.3 | 4 |
| 10 | – | 7.2 ± 2.3 | 5 |
| 10 | + | 4.9 ± 2.9[d] | 4 |

[a] Phenobarbital induction, 1.8% enflurane, 2 hr.
[b] Symbols: (–), no external heating during exposure; (+), external heating.
[c] Values are $\overline{X}$ ± SD.
[d] $P < 0.05$ versus 14% $O_2$ exposures.

Table 2. Effect of Oxygen Tension and External Heating to Help Maintain Normothermia on Serum Metabolite Levels Immediately after Exposure to 0.5% Halothane[a]

| Oxygen concentration (% $O_2$) | External heating[b] | Serum fluoride (μM) | Serum TFA[c] (μM) | *n* |
|---|---|---|---|---|
| 14 | – | 8.7 ± 5.6 | 783 ± 207 | 4 |
| 14 | + | 8.3 ± 3.4 | 683 ± 260 | 5 |
| 10 | – | 19.2 ± 5.4 | 495 ± 64 | 4 |
| 10 | + | 37.4 ± 14.8[d] | 309 ± 105[e] | 5 |

Values are $\overline{X}$ ± SD.
[a] Phenobarbital induction, 2 hr exposure.
[b] Symbols: (–), no external heating during exposure; (+), external heating.
[c] TFA, trifluoroacetic acid.
[d] $P < 0.05$ versus all others.
[e] $P < 0.05$ versus 14% $O_2$ exposures.

flurane during exposure at different oxygen concentrations and body temperatures is investigated as well as the chronology of the ensuing of hepatotoxicity. Also contrasted are differences between the two models in so far as phenobarbital pretreatment and heating of the animals during anesthesia determine the incidence and severity of hepatic injury. Results from exposure to the classic hepatochemotoxin carbon tetrachloride ($CCl_4$) (7), or severe hypoxia (5% $O_2$) alone are also compared with the two anesthetic-related models.

## Materials and Methods

### *Animals*

Male Sprague–Dawley rats (250–350 g) from Hilltop Lab Animals (Scottsdale, PA) were housed in stainless steel cages in an isolated room and maintained on a 12-hr light/dark cycle at a temperature of 22°C. Standard laboratory rat chow and water were provided ad libitum. Hepatic biotransformation enzymes were induced via a single intraperitoneal injection of 100 mg/kg PB followed by 5 days of 1 mg/ml of PB in the drinking water.

### *Exposure Conditions*

Exposures of the rats to the anesthetics or hypoxia were carried out on the sixth day for 2 hr in a 180-L plexiglass exposure chamber equipped with a circulating fan. Halothane (Ayerst Laboratories, New York, NY) and enflurane (Ohio Medical Products, Madison, WI) were delivered at a flow rate of 6 L/min via a Vernitrol vaporizer (Ohio Medical Products, Madison, WI), mixing $N_2$ and $O_2$ to produce desired atmospheres. Concentrations of the anesthetics were monitored by gas chromatography and oxygen tensions with a polargraphic oxygen electrode, as previously described (6). Warming the animals to help maintain body temperature was accomplished with two 20-W heaters attached to the underside of a metal plate that served as the floor of the chamber and upon which the animals laid during anesthesia. Animals were positioned during anesthesia so that they were separated from each other by a space of approximately 2 cm. Air temperatures in the chamber during exposures were 24–26°C without the heaters on and 31–32°C with heating. The floor of the chamber was a constant 35°C with the heaters on. Body temperatures were monitored using rectal probes attached to a telethermometer (Yellow Springs Instruments, Yellow Springs, OH).

The EHH model included PB pretreatment of the animals followed by exposure to 1.5–1.8% enflurane at 10% $O_2$ for 2 hr with heating to help maintain body temperature. The HH model was produced by exposure of PB-pretreated rats to 1% halothane, 14% $O_2$ for 2 hr. As a positive control for a hepatic chemotoxin, previously untreated rats were given 1 ml/kg $CCl_4$ dissolved in an equal volume of corn oil by oral gavage. Severe hypoxia exposures were carried out at 5% $O_2$ for 2 hr with or without the chamber plate heaters on.

At appropriate times, animals were killed by cervical dislocation, and blood was drawn from the inferior vena cava at the juncture with the hepatic vein. Serum was obtained by centrifugation and stored at 4°C. Serum glutamate pyruvate transaminase (SGPT) levels were determined (Sigma Technical Bulletin No. 55-UV; Sigma Chemical Company, St. Louis, MO) and expressed in Wroblewski–LaDue (W–L) units. Serum inorganic fluoride was measured with Orion selective ion electrodes (Orion Research, Cambridge, MA) and serum trifluoroacetic acid (TFA) levels by a gas chromatographic headspace technique (8).

Sections of hepatic tissue from the various treatment groups were fixed in 10% phosphate buffered

Table 3. Effect of External Heating to Help Maintain Normothermia on Serum Metabolite Levels Immediately after Exposure in the Halothane–Hypoxia Model[a]

| External heating[b] | Serum fluoride ($\mu M$) | Serum TFA[c] ($\mu M$) |
|---|---|---|
| – | 21 ± 4 | 1,240 ± 530 |
| + | 28 ± 6 | 950 ± 310 |

$n = 4$.

[a] Phenobarbital induction, 1% halothane, 14% $O_2$, 2 hr.

[b] Symbols: (–), no external heating during exposure; (+), external heating.

[c] TFA, trifluoroacetic acid.

[d] Values are $\bar{X} \pm$ SD and are not significantly different.

Table 4. Time Course of Development of Hepatic Injury after Exposure to Anesthetic Models or $CCl_4$

| Time[a] (hr) | SGPT (W–L units/ml) HH[b] | SGPT (W–L units/ml) $CCl_4$[c] | SGPT (W–L units/ml) EHH[d] |
|---|---|---|---|
| 0 | 24 ± 3<br>(4) | — | 205 ± 273[e]<br>(14) |
| 2 | 28 ± 10<br>(4) | 26 ± 1<br>(3) | — |
| 6 | 29 ± 5<br>(4) | 39 ± 12<br>(3) | 232 ± 190[e]<br>(3) |
| 12 | 54 ± 31<br>(4) | 114 ± 95<br>(4) | — |
| 24 | 105 ± 70[f]<br>(9) | 289 ± 414<br>(4) | 288 ± 287<br>(9) |

All values are $\bar{X} \pm$ SD.

SGPT in untreated animals is 24 ± 6 W–L units/ml.

Number of animals in parentheses.

[a] Time after exposure or dosing.

[b] Phenobarbital pretreatment, 1% halothane, 14% $O_2$, 2 hr.

[c] 1 ml/kg orally 50:50 in corn oil.

[d] Phenobarbital pretreatment, 1.5–1.8% enflurane, 10% $O_2$, 2 hr, with external heating to help maintain normothermia.

[e] $P < 0.05$ vs other values at same time point.

[f] $P < 0.05$ vs 0, 2, 6 hr post HH exposure.

formalin and processed into 7-$\mu$m thick slices that were stained with hemotoxylin and eosin for subsequent histopathologic evaluation.

### *Experimental Protocol*

The effects on the metabolism of halothane and enflurane of decreasing oxygen tension and heating the rats to help maintain normothermia during anesthesia was evaluated by measuring serum TFA and fluoride ion levels immediately after exposure. TFA production is a measure of the oxidative biotransformation of halothane, while fluoride levels are an indication of reductive metabolism (9). Enflurane undergoes biotransformation only by an oxidative pathway, releasing fluoride ions (9). Thus serum fluoride levels after enflurane anesthesia are considered a marker of its oxidative metabolism. Animals ($n$ = 4 or 5) were exposed to 1.8% enflurane or 0.5% halothane at 14 or 10% $O_2$ with or without external heating to help maintain body temperature. Halothane concentration was reduced to 0.5% in order for the animals to survive a 2-hr exposure at 10% $O_2$. Animals ($n$ = 4) were also exposed under conditions of the HH model (1% halothane, 14% $O_2$, 2 hr) with or without external heating

Table 5. Requirement of Prior Hepatic Enzyme Induction for Development of Hepatotoxicity after Exposure to Anesthetics or Severe Hypoxia Alone

| Treatment | Time[a] (hr) | SGPT (W–L units/ml) Noninduced[b] | SGPT (W–L units/ml) Induced[c] |
|---|---|---|---|
| HH[d] | 24 | 25 ± 9<br>(9) | 105 ± 70[g]<br>(9) |
| EHH[e] | 0 | 166 ± 228<br>(4) | 205 ± 273<br>(14) |
| Severe hypoxia[f] | 0 | 52 ± 20<br>(5) | 81 ± 57<br>(4) |

All values are $\bar{X} \pm$ SD.

SGPT in untreated animals is 24 ± 6 W–L units/ml.

Number of animals is in parentheses.

[a] Time after end of exposure.

[b] No phenobarbital pretreatment.

[c] Phenobarbital pretreatment.

[d] 1% halothane, 14% $O_2$, 2 hr.

[e] 1.5–1.8% enflurane, 10% $O_2$, 2 hr, with external heating to help maintain normothermia.

[f] 5% $O_2$, 2 hr, with external heating.

[g] $P < 0.05$ vs noninduced value; other induced vs noninduced values not significantly different.

Table 6. Role of External Heating for Development of Hepatotoxicity after Exposure to Anesthetics or Severe Hypoxia Alone

| Treatment | Time[a] (hr) | SGPT (W–L units/ml) Without external heating[b] | SGPT (W–L units/ml) With external heating[b] |
|---|---|---|---|
| HH[c] | 0 | 24 ± 3<br>(4) | 21 ± 2<br>(3) |
| | 24 | 105 ± 70<br>(9) | 106 ± 45<br>(4) |
| EHH[d] | 0 | ND | 205 ± 273<br>(14) |
| | 24 | 27 ± 5<br>(9) | 288 ± 287[f]<br>(9) |
| Severe hypoxia[e] | 0 | 24 ± 3<br>(4) | 81 ± 57[f]<br>(4) |

ND, not determined.

All values are $\bar{X} \pm$ SD.

SGPT in untreated animals is 24 ± 6 W–L units/ml.

Number of animals is in parentheses.

[a] Time after end of exposure.

[b] During 2 hr exposure.

[c] Phenobarbital induction, 1% halothane, 14% $O_2$, 2 hr.

[d] Phenobarbital induction, 1.5–1.8% enflurane, 10% $O_2$, 2 hr.

[e] Phenobarbital induction, 5% $O_2$, 2 hr.

[f] $P < 0.05$ vs hypothermic values.

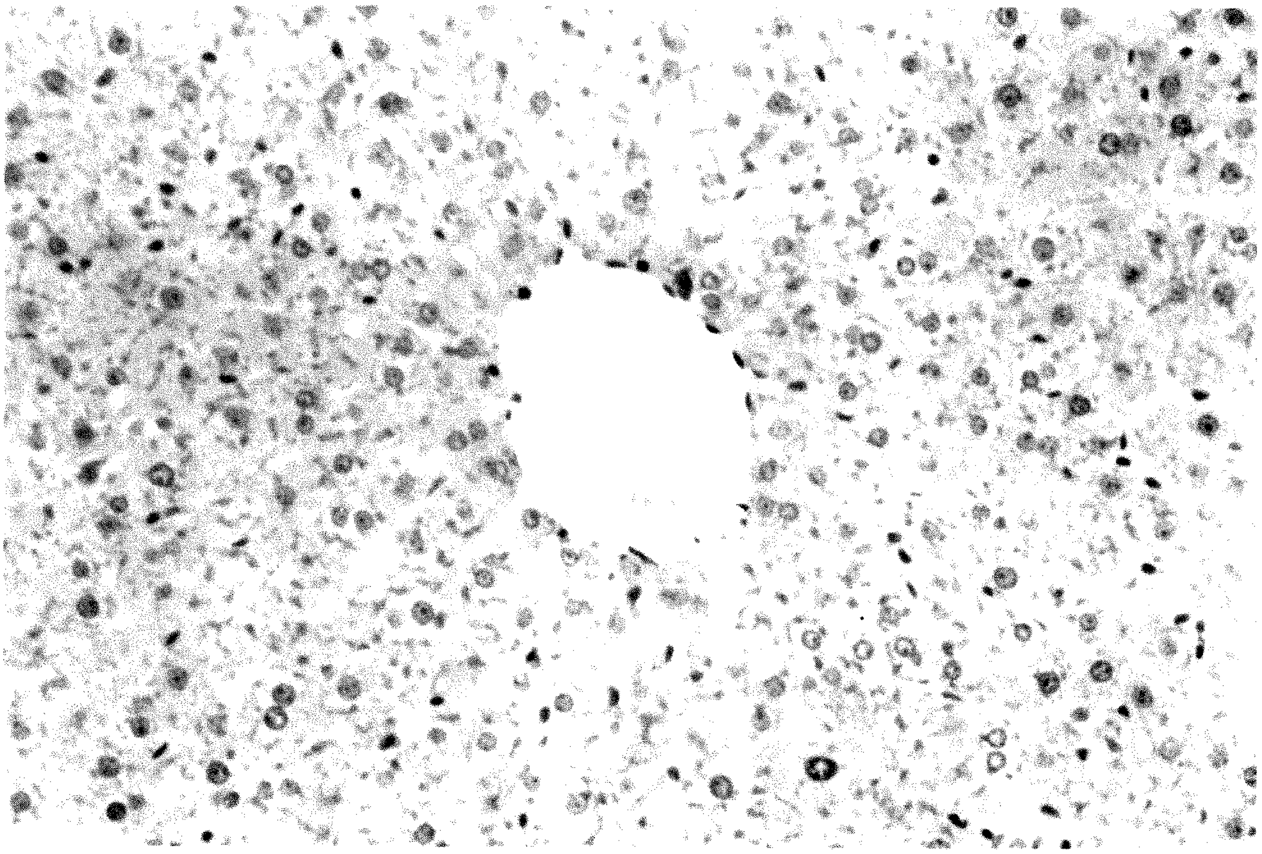


Figure 1. Photomicrograph of a rat liver section immediately after exposure to the halothane hypoxia model (125× H & E).

in order to observe the effects of maintaining body temperature during halothane exposure on serum metabolite levels immediately after anesthesia.

The temporal evolution of hepatotoxicity, as measured by elevations in SGPT, was compared between the HH and EHH models and a group of rats given $CCl_4$ by killing the animals at various times up to 24 hr after treatment ($n$ = 3–14 per time point).

The necessity of prior hepatic enzyme induction and heating of the animals during exposure in order to obtain hepatic lesions was evaluated in both the HH and EHH models ($n$ = 4–14 in each group). Because an almost immediate increase in SGPT is indicative of a hypoxic/anoxic liver injury (10), blood samples were taken at the end of the enflurane exposures. In evaluating the requirement of maintaining normothermia in the enflurane model, blood samples were also collected 24 hr after exposure. The necessity of PB pretreatment and external heating was also evaluated for the development of hepatic injury immediately after exposure to severe hypoxia (5% $O_2$) alone ($n$ = 4 or 5).

### *Statistical Analysis*

Comparison of values was made using analysis of variance (ANOVA) or a one-tailed Student's $t$-test when applicable. For SGPT, the log of the value was used for analysis because standard deviations increased with increasing means.

## Results

### *Effect of Anesthesia on Body Temperature*

Both halothane (1%) and enflurane (1.5–1.8%) anesthesia caused similar time-dependent decreases in rectal temperatures of 7.9 ± 1.4°C ($\overline{X} \pm$ SD, $n = 11$) over 2 hr in rats that received no thermal support, while the temperatures of animals externally heated to help maintain normothermia decreased only 1.2 ± 0.8°C ($\overline{X} \pm$ SD, $n = 10$).

### *Effect of Inspired Oxygen Tension and Body Temperature during Anesthetic Exposure on the Degree of Biotransformation*

When animals were heated to help maintain body temperature and inspired 10% $O_2$ during exposure to enflurane (1.8%) or halothane (0.5%), the levels of

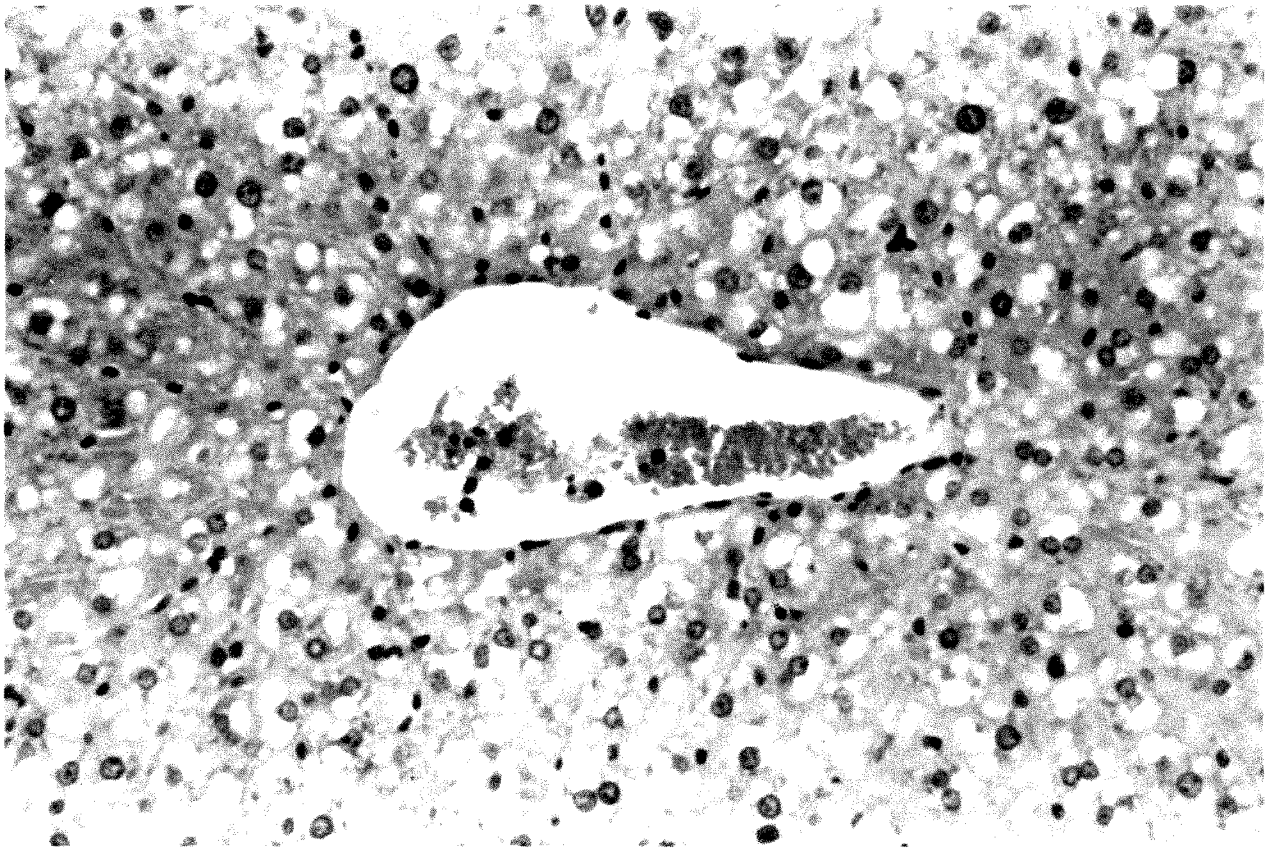


Figure 2. Photomicrograph of a liver section from a rat immediately after exposure to the enflurane-hypoxia heating model (125 × H & E).

oxidative biotransformation of each anesthetic were significantly less than levels occurring during exposures at 14% $O_2$ under either hypothermic or temperature-supported conditions (Tables 1,2). The reductive metabolism of halothane, as indicated by serum fluoride levels, increased twofold when the oxygen concentration was reduced from 14 to 10% in hypothermic rats and fourfold if the oxygen was reduced from 14 to 10% in temperature-supported animals (Table 2). Heating to help maintain normothermia during halothane exposure at 14% $O_2$ had little effect on serum fluoride and TFA levels when compared to hypothermic exposures, regardless of whether the halothane concentration during exposure was 0.5% (Table 2) or 1% (Table 3).

## *Time Course of Hepatic Injury*

The time course for development of hepatic damage in the HH model paralleled that observed in rats given $CCl_4$ (Table 4). However, SGPT values in EHH-exposed rats increased immediately after exposure and remained elevated even 24 hr after exposure. The immediate increase in SGPT values is indicative for a hepatic injury resulting from a hypoxic/anoxic episode (10,11) and mimics results observed in animals exposed to 2 hr of severe hypoxia (5% $O_2$) with external heating (Table 5).

## *Effect of Phenobarbital Pretreatment on Anesthetic-Induced Hepatotoxicity*

Prior induction of hepatic enzyme levels with PB proved necessary for the development of liver injury in the HH model as indicated by the fourfold increase in 24-hr SGPT levels in the PB-pretreated animals, but not in noninduced animals (Table 5). In the EHH model, pretreatment with PB was not necessary for hypoxic/anoxic hepatic injury to occur, as expressed by an immediate increase in SGPT after exposure. Approximately 10–20% of the animals exposed to EHH had SGPT levels in the range of 1000–3000 units/ml and were omitted from the table to minimize data variation for comparative purposes. Phenobarbital pretreatment was also not necessary to produce the immediate hepatic injury associated with exposure to severe hypoxia (5% $O_2$) plus external heating.

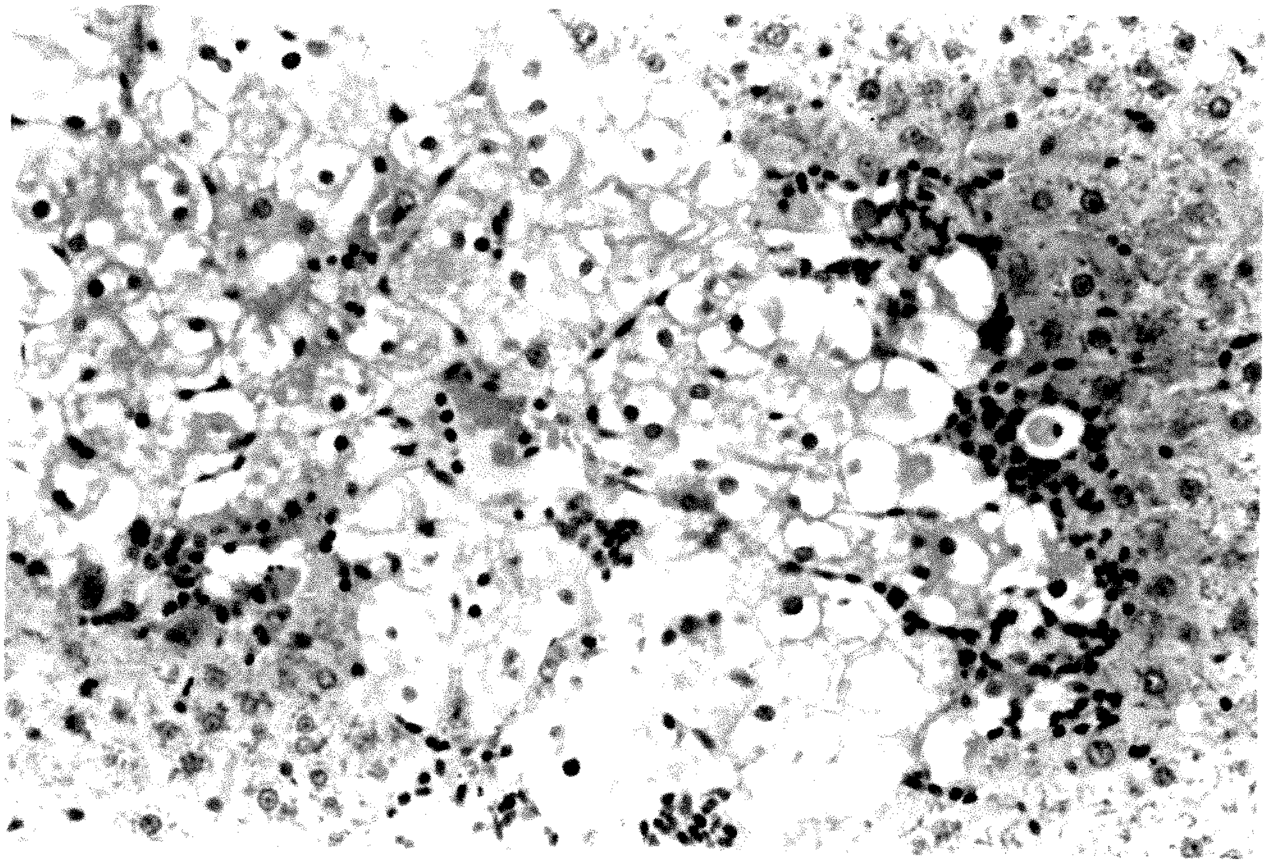


Figure 3. Photomicrograph of a liver section 24 hr after exposure of the rat to halothane-hypoxia model (125× H & E).

### Effect of Body Temperature on Anesthetic-Induced Hepatic Injury

External heating to help maintain normothermia had no effect on the hepatic injury resulting from exposure of phenobarbital-pretreated rats to 1% halothane at 14% $O_2$ for 2 hr (Table 6). However, the hepatotoxicity associated with exposure to 1.5–1.8% enflurane at 10% $O_2$ for 2 hr was dependent upon maintenance of the rat's body temperature. A similar requirement of external heating for the expression of hepatotoxicity was observed with the animals exposed to severe hypoxia (5% $O_2$) for 2 hr.

### Pathologic Observations

In the HH model hepatic architecture was normal immediately after exposure to halothane (Fig. 1), while immediately after exposure to EHH a watery vacuolization of hepatocytes occurred in centrilobular areas (Fig. 2). This water vacuolization, which is indicative of hypoxic/anoxic liver injury (11), was also observed immediately after exposure to severe hypoxia combined with external heating. The watery vacuolization stained negatively for fat utilizing an $OsO_4$ stain on frozen sections. The HH model showed gradual progression to the primarily vacuolative injury observed 24 hr after exposure (Fig. 3). With the EHH model, frank coagulative hepatic necrosis was observed in some animals within 6 hr of exposure. Coagulative necrosis was also observed in most of the samples taken 24 hr after EHH in addition to a vacuolative injury similar to that seen in the 24-hr HH samples (Fig. 4).

## Discussion

Major differences between the previously reported HH model (3,4) and the enflurane-induced hepatotoxicity model of Shingu et al. (1,2) were noted. The chronology of development of liver lesions, the conditions needed for the models to produce hepatic injury, and the pathologic characterization of the initial injuries were quite dissimilar. The HH model followed a time course of SGPT elevation and appearance of pathologic changes that is similar to $CCl_4$-induced hepatotoxicity, while EHH produced a classic hypoxic/anoxic injury immediately after exposure. The HH model required PB pretreatment for expression

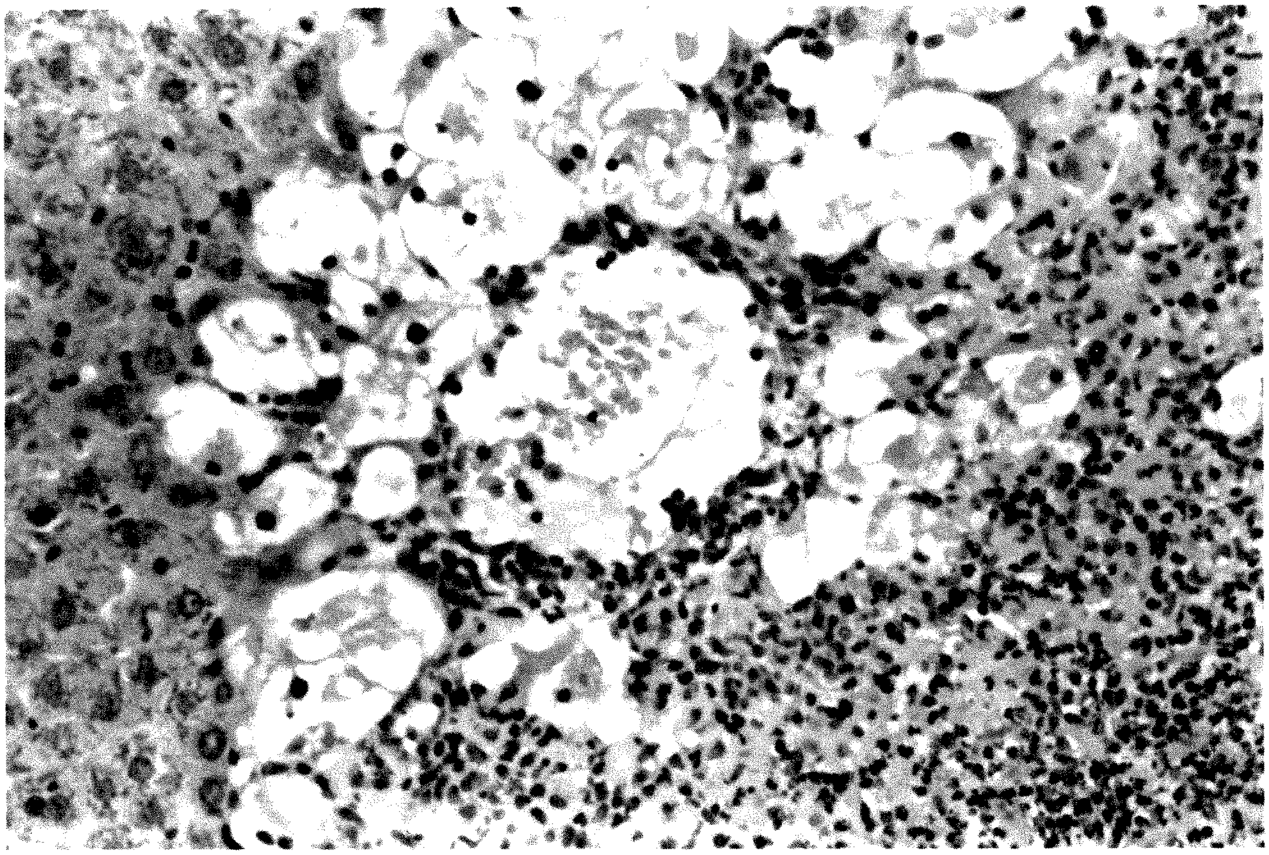


Figure 4. Photomicrograph of a liver section 24-hr after exposure of the rat to enflurane-hypoxia-heating model (125× H & E).

of hepatic injury; the EHH model did not. Hepatotoxicity resulting from enflurane exposure at 10% $O_2$ required heating of the animals during anesthesia. Whether or not the animals were heated seemed to have little effect on the HH model.

Hypothermia during HH anesthesia in rats has been reported and alluded to as a hepatoprotective mechanism (12). Although our animals typically demonstrated a time-dependent temperature depression of 7–9°C during exposure to HH, they still developed a hepatic lesion. Shingu et al. also found halothane to be hepatotoxic in rats when hypothermia was allowed to develop during exposure in 10% $O_2$, while other anesthetics tested did not cause hepatic injury under the same exposure conditions (13). In our experiments, even the animals that were heated during anesthetic exposure developed a 0.5–2°C drop in body temperature. This mild hypothermia was not sufficient to affect lesion development in either of the anesthetic models. But, our allowing the slight temperature depression to occur did avoid heating the rats above normothermia, which can greatly exacerbate the hepatic injury resulting from HH exposure (12).

External heating to help maintain body temperature greatly increased the hypoxic state of the liver when the rats were exposed to the anesthetics in 10% $O_2$ as indicated by the decreased oxidative metabolism of halothane and enflurane and increased reductive metabolism of halothane (Table 1,2). The increase in hepatic hypoxia due to external heating was much less pronounced when the rats were exposed in 14% $O_2$ (Tables 1–3). This enhanced state of hypoxia/anoxia in the liver created by the combination of a 10% $O_2$ atmosphere coupled with external heating during anesthesia was a prerequisite for the enflurane-induced hepatic injury (EHH). In the HH model, external heating to help maintain normothermia during exposure did not alter the level of toxicity obtained at 24 hr, nor was any elevation in SGPT noted immediately after exposure as was observed with hypoxic/anoxic liver injury (Table 6).

Induction of hepatic drug metabolizing enzymes by PB pretreatment was necessary to obtain hepatotoxicity in the halothane model, but not with the EHH model or with exposure to severe hypoxia (5% $O_2$) with external heating (Table 5). This lends credence to the theory that enhanced biotransformation of halothane to reactive intermediates resulting from enzyme induction and mildly hypoxic exposure conditions is the mechanism of hepatotoxicity in the HH model (14). It would also appear that pretreatment with PB is not necessary for the production of a hepatotoxic hypoxic/anoxic state within the liver during exposure under the conditions of the EHH model or with severe hypoxia (5% $O_2$) plus heating.

Striking differences between the two models of anesthetic-induced hepatotoxicity are evident in the time courses of changes in SGPT levels and in development of morphologic liver damage. In the HH model, the associated hepatic lesion followed a course of development similar to that produced by administration of the chemotoxin $CCl_4$. Normal liver architecture and levels of serum enzymes were present immediately after HH exposure (Fig. 1, Table 4). Initial changes in centrilobular hepatocytes and slight increases in SGPT were not evident until several hours later and subsequently progressed to the primarily vacuolative centrilobular injury with the associated elevations in SGPT observed 24 hr after exposure (Fig. 3). The EHH model, on the other hand, consistently demonstrated elevations in SGPT and watery vacuolization of centrilobular hepatocytes immediately after exposure, both of which are indicative of hypoxic/anoxic liver injury (10,11) (Fig. 2, Table 4). This centrilobular lesion rapidly progressed to a frank coagulative necrosis within 6 hr in most of the animals exposed to EHH. Although the immediate elevations in SGPT caused by exposure to severe hypoxia (5% $O_2$) with external heating are only one-third to one-half the levels produced by the EHH model, the similarities between the two experimental groups in changes in serum enzymes and liver morphology just after exposure would indicate involvement of related mechanisms. The differences in SGPT values between the EHH and severe hypoxia plus heating groups are probably due only to differing degrees of hepatic hypoxia/anoxia generated during exposure.

The animals used in these experiments demonstrated an extremely wide variability in their hepatotoxic response to EHH exposures, as indicated by SGPT values. This led to standard deviations as large as the means in most cases, even with omission of very high values (1000–3000 units/ml) that occurred in 10–20% of the EHH-treated animals. Obviously, a very inconsistent degree of hepatic hypoxia/anoxia was generated during exposure to EHH. Although the SGPT values are extremely variable, the time course of SGPT elevations and the liver morphology resulting from EHH exposure are indicative of hypoxic/anoxic-induced hepatic damage. Even with the large standard deviations, the data still serve the intended purpose of a qualitative comparison of the requirements for the expression of hepatotoxicity and its chronologic development in the two anesthetic models studied.

The original studies on the hypoxic/anoxic models of anesthetic-induced hepatic damage reported hepatotoxicity at a fraction of MAC (2). We also found that 1% enflurane (0.45 MAC) produced hepatic injury in our EHH exposures (data not shown). Animals exposed to this level of anesthetic also demonstrated watery vacuolization of centrilobular hepatocytes immediately after exposure with 20% of these animals having SGPT levels in excess of 1000 units/ml. This further attests to the severity of the effect of anesthetic exposure at 10% $O_2$ combined with external heating upon oxygenation of the liver.

An elevation in SGPT immediately after exposure has been reported to occur in models of volatile anesthetic-induced hepatotoxicity involving pretreatment with triiodothyronine (15,16). This sudden increase in SGPT, coupled with the known stimulation of intrahepatic oxygen consumption by triiodothyronine (17), indicates that the triiodothyronine model also produces liver damage by hypoxic/anoxic mechanisms. In another reported model producing coagulative hepatic necrosis in male rats after a 2-hr exposure to 0.5% halothane in 8% $O_2$, prior fasting of the animals was a prerequisite to produce hepatic damage (18). Fasting can also be considered an additional stress upon the liver, as glutathione levels are greatly reduced, leaving the hepatocytes more vulnerable not only to chemical injury (19) but also the lipid peroxidation (20) and watery vacuolization (11) that accompanies hypoxic/anoxic injury. In addition, fasting severely depletes hepatic glycogen stores in rats (21). Thus with decreased energy sources and reduced glutathione levels, the hepatocytes are more prone to insult by hypoxia.

Halothane can undergo reductive metabolism forming free radicals in vitro (22) and in vivo (5) that bind to subcellular macromolecules (14) and cause injury to subcellular enzyme systems (23). Pretreatment of rats with a variety of free radical scavengers and cytochrome P-450 inhibitors has been shown to have a protective action on halothane-induced injury in rats (24–28). Halothane can also cause fatty change and necrosis in the liver of unpretreated male and female rats when administered at very low concentrations (50 ppm) at ambient oxygen tensions over long (12-week) periods of time (29), as well as in dogs and monkeys repeatedly exposed to anesthesia producing concentrations delivered in 100% $O_2$ (30). Although it is presently not possible to prove the mechanism of halothane-induced hepatic injury in the rat HH model, these facts, combined with the results reported here, indicate a chemotoxic mechanism of hepatotoxicity with HH rather than a hypoxic/anoxic mechanism as seen with the EHH model.

## References

1. Shingu K, Eger EI II, Johnson BH. Hypoxia may be more important than reductive metabolism in halothane-induced hepatic injury. Anesth Analg 1982;61:824–7.
2. Shingu K, Eger EI II, Johnson BH, Van Dyke RA, Lurz FW, Harper MH, Cheng A. Hepatic injury by anesthetic agent in rats. Anesth Analg 1983;62:140–5.
3. McLain GE, Sipes IG, Brown BR Jr. An animal model of halothane hepatotoxicity: roles of enzyme induction and hypoxia. Anesthesiology 1979;51:321–6.
4. Cousins MJ, Sharp JH, Gourlay GK, Adams JF, Haynes WD, Whitehead R. Hepatoxicity and halothane metabolism in an animal model with application for human toxicity. Anaesth Intens Care 1979;7:9–24.
5. Plummer JL, Beckwith AL, Bastin FN, Adams JF, Cousins JM, Hall P de la M. Free radical formation in vivo and hepatotoxicity due to anesthesia with halothane. Anesthesiology 1982;57:160–6.
6. Lind RC, Gandolfi AJ, Sipes IG, Brown BR. The involvement of endotoxin in halothane-associated liver injury. Anesthesiology 1984;61:544–50.
7. Zimmerman HJ. Direct (toxipathic) hepatotoxins: haloalkanes and elemental phosphorus. In: Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. New York: Appleton-Century-Crofts, 1978;198–219.
8. Maiorino RM, Gandolfi AJ, Sipes IG. Gas chromatographic method for the halothane metabolites, trifluoracetic acid and bromide in biological fluids. Analyt Tox 1980;4:250–4.
9. Vaughan RW, Sipes IG, Brown BR. Minireview: role of biotransformation in the toxicity of inhalation anesthetics. Life Sciences 1978;23:2447–62.
10. Frederiks WM, Myagkaya GL, Bosch KS, Fronik GM, Van Veen H, Vogels IMC, James J. The value of enzyme leakage for the prediction of necrosis in liver ischemia. Histochemistry 1983;78:459–72.
11. Trowell OA. The experimental production of watery vacuolation of the liver. J Physiol 1946;105:268–97.
12. Ford D, Coyle DE. Effect of body temperature on the halothane-hypoxia-induction model of halothane hepatitis. Anesthesiology 1983;59:A222.
13. Shingu S, Eger E, Johnson AB, Van Dyke RA, Lurz FW, Cheng A. Effect of oxygen concentration, hyperthermia, and choice of vendor on anesthetic-induced hepatic injury in rats. Anesth Analg 1983;62:146–50.
14. Sipes IG, Gandolfi AJ, Brown BR. Halothane-associated hepatitis: evidence for direct hepatotoxicity. In: M. Davis, JM Tredger, R. Williams (eds). Drug reactions and the liver. London: Pitman Medical Ltd, 1981:219–31.
15. Wood M, Berman ML, Harbison RD, Hoyle P, Phythyon JM, Wood AJJ. Halothane-induced hepatic necrosis in triiodothyronine-pretreated rats. Anesthesiology 1980;52:470–6.
16. Berman ML, Kuhnert L, Phythyon JM, Holaday DA. Isoflurane and enflurane-induced hepatic necrosis in triiodothyronine-pretreated rats. Anesthesiology 1983;58:1–5.
17. Israel Y, Videla L, Bernstein J. Liver hypermetabolic state after chronic ethanol consumption. Fed Proceed 1975;34:2052–9.
18. Van Dyke RA. Hepatic centrilobular necrosis in rats after exposure to halothane, enflurane, or isoflurane. Anesth Analg 1982;61:812–9.
19. Jaeger RJ, Conolly RB, Murphy SD. Effect of 18 hr fast and glutathione depletion on 1,1-dichloroethylene-induced hepatotoxicity and lethality in rats. Exper Mol Pathol 1974;20:187–98.
20. Jennische E. Possible influence of glutathione on postischemic liver injury. Acta Pathol Microbiol Immunol Scand 1984;92A:55–64.
21. Freminent A. Comparison of glycogen store in rats and guinea pigs. Effects of anesthesia, fasting and re-feeding. Comp Biochem Physiol 1981;69B:655–63.
22. Tomasi A, Billing S, Garner A, Slater TF, Albano E. The metabolism of halothane by hepatocytes: a comparison between free radical spin trapping and lipid peroxidation in relation to cell damage. Chem Biol Interactions 1983;46:353–68.
23. Krieter PA, Van Dyke RA. Cytochrome P-450 and halothane metabolism. Decrease in rat liver microsomal P-450 in vitro. Chem Biol Interactions 1983;44:219–35.
24. Jee RC, Sipes IG, Gandolfi AJ, Brown BR Jr. Factors influencing halothane hepatotoxicity in the rat hypoxic model. Toxicol Appl Pharmacol 1980;52:267–77.
25. Siegers CP, Fruhling A, Younes M. Influence of dithiocarb, (+)-Catechin and silybine on halothane hepatotoxicity in the hypoxic rat model. Acta Pharmacol Toxicol 1983;53:125–9.
26. Eade OE, Millward-Sadler GH, Lucas K, Mitchell J, Wright R. Hepatic necrosis in rats following halothane administration: protective effect of diethyldithiocarbamate. Scand J Gastroenterol 1980;15:859–64.
27. Nastaincyzk W, Rendic S, Ullrich V, Kruger R. Hemmung Halothane-induzierter Leberzellnekrosen bei Ratten durch Metyrapon. Anaesthesist 1982;31:181–4.
28. Plummer JL, Wanwimolruk S, Jenner MA, Hall P de la M, Cousins JM. Effects of cimetidine and ranitidine on halothane metabolism and hepatotoxicity in an animal model. Drug Metab Dispos 1984;12:106–10.
29. Plummer JL, Hall P de la M, Cousins MJ, Bastin FN, Hasley AH. Hepatic injury in rats due to prolonged sub-anesthetic halothane exposure. Acta Pharmacol Toxicol 1983;53:16–22.
30. Clark GC, Kesterson JW, Coombs DW, Cherry CP, Prentice DE, Kohn FE. Comparative effects of repeated and prolonged inhalation exposure of beagle dogs and cynomolgus monkeys to anaesthetic and subanaesthetic concentrations of enflurane and halothane. Acta Anaesthesiol Scand 1979;S71:1–11.

ANESTH ANALG
1985;64:964–70

# Antiarrhythmic Effect of Diltiazem During Halothane Anesthesia in Dogs and in Humans

Naofumi Iwatsuki, MD, Masato Katoh, MD, Katsuhiko Ono, MD, and Keisuke Amaha, MD

IWATSUKI N, KATOH M, ONO K, AMAHA K. Antiarrhythmic effect of diltiazem during halothane anesthesia in dogs and in humans. Anesth Analg 1985;64:964–70.

*The antiarrhythmic effects of diltiazem (DL), a slow channel inhibitor, were evaluated in the presence of epinephrine–halothane-induced arrhythmias in dogs, of premature ventricular contractions (PVCs) during anesthesia in patients ($n = 10$), and of tachyarrhythmias with associated atrial fibrillation (AF) during anesthesia in patients ($n = 9$). The arrhythmogenic dose of epinephrine (ADE) during one MAC of halothane in dogs was increased from 1.13 ± 0.21 to 3.14 ± 0.89* $\mu g \cdot kg^{-1} \cdot min^{-1}$ *by the administration of 0.3 mg/kg of DL. This suggests that DL significantly increases the threshold for the induction of arrhythmias associated with epinephrine and halothane. In 10 patients, PVCs that appeared spontaneously during halothane anesthesia were eliminated by the intravenous administration of DL (0.1 mg/kg). With an additional nine patients who had had AF preoperatively and suffered tachyarrhythmias during anesthesia, the intraoperative intravenous administration of DL significantly decreased heart rate (to less than 100 beats/min) within 10–15 min. Diltiazem is an effective means for the treatment of PVCs and AF-mediated tachyarrhythmias during anesthesia. Because of the pharmacologic properties of DL (e.g., depressing sinus and atrioventricular (AV) node function), DL should be used with caution in patients with a sick sinus syndrome or an AV block, or in the presence of β-adrenergic antagonists.*

Key Words: HEART—arrhythmias. PHARMACOLOGY—diltiazem. ANESTHETICS, VOLATILE—halothane.

Diltiazem hydrochloride, a slow channel inhibitor, inhibits the movement of calcium ions ($Ca^{2+}$) across cell membranes. Diltiazem (DL) thus relaxes vascular smooth muscle, depresses myocardial contractility, and depresses sinus and atrioventricular node function (1–6). Accordingly, DL has been recommended for the treatment of various types of cardiovascular disorders, including coronary vasospasm, angina, and hypertension (6–11).

The antiarrhythmic effect of DL has been studied using microelectrodes (12). Its effect on epinephrine- and ouabain-induced arrhythmias (13), on ischemia-mediated ventricular fibrillation (14,15), and on reentrant ventricular arrhythmias (16) has been evaluated in experimental animals. The clinical efficacy of the antiarrhythmic effect of DL only recently has begun to be studied. DL, along with another slow channel inhibitor, verapamil, has been reported to be effective in the treatment of supraventricular tachycardia (SVT) (17–19).

The effects of DL on arrhythmias other than SVT as well as on arrhythmias occurring during general anesthesia, however, have not been evaluated. We, therefore, examined the effects of DL upon halothane–epinephrine-induced arrhythmias in dogs, as well as the effects of DL on premature ventricular contractions (PVCs) and tachyarrhythmias mediated by atrial fibrillation during anesthesia in patients.

## Methods

### *Animal Study*

Six mongrel dogs weighing 10.8 ± 2.2 kg (SD) were anesthetized with thiopental (25 mg/kg intravenously) and intubated with a cuffed endotracheal tube. Mechanical ventilation was provided by a volume controlled animal ventilator (AIKA R-60) to maintain a pH of 7.36–7.46, a $Pa_{CO_2}$ of 32–37 mm Hg, and a $Pa_{O_2}$ of 400–647 mm Hg with 100% oxygen. End-tidal $CO_2$ concentrations were continuously monitored with an infrared $CO_2$ analyzer (Morgan 901-MK 2). Anesthesia was maintained with one MAC of halothane (0.87%) by a Fluotec Mark III vaporizer.

---

Received from the Department of Anesthesiology, Tohoku University School of Medicine, Sendai, Japan. Accepted for publication May 8, 1985.

Addresss correspondence to Dr. Iwatsuki, Department of Anesthesiology, Tohoku University School of Medicine, 1-1 Seiryo-machi, Sendai 980, Japan.

© 1985 by the International Anesthesia Research Society

A cannula placed in the femoral artery was connected to a force transducer (Statham P23Db) for intraarterial pressure monitoring. Another cannula in the femoral vein was used for intravenous fluid administration (4 ml·kg$^{-1}$·hr$^{-1}$ of a crystalloid solution) and for injection of drugs. A pulmonary artery catheter was inserted through a left neck vein for measurement of pulmonary vascular pressure. Lead II of the ECG was continuously monitored on an oscilloscope with P–Q intervals measured by recording the ECG on paper at a paper speed of 100 mm/sec when necessary.

After 40–60 min of stabilization under one MAC of halothane, the arrhythmogenic dose of epinephrine (ADE) was determined by the method described by Pace et al. (20). Epinephrine (E) diluted to 50 $\mu$g/ml in a normal saline was infused by an infusion pump at rates of 0.11, 0.15, 0.21, 0.30, 0.42, 0.58, 0.82, and 1.1 ml/min. When four or more PVCs developed during a 3-min E infusion, this concentration of E was considered to be the ADE expressed as $\mu$g·kg$^{-1}$·min$^{-1}$. If four or more PVCs did not occur during the 3-min infusion of E at one rate of infusion, the rate of infusion was increased to the next higher step after a 10-min recovery period. This procedure was repeated until the ADE was obtained. After the determination of ADE in the absence of DL (i.e., control), each dog was given 0.1 mg/kg of DL intravenously, and the same procedure to determine ADE was repeated starting at the rate that induced ADE of the control. At 30 min after the determination of ADE under 0.1 mg/kg of DL, a 0.3 mg/kg dose of DL was given to the dog, and the same procedure to determine ADE was repeated starting from the rate that induced ADE under 0.1 mg/kg of DL.

Paired *t*-tests were used for statistical analysis; a statistically significant difference was assumed when *P* was less than 0.05.

### *Clinical Study*

The effects of DL on PVCs were evaluated in 10 patients ranging in age from 3 to 66 yr. DL, 0.1 mg/kg, was injected intravenously in bolus when PVCs developed and continued for more than 5 min under halothane anesthesia. When PVCs developed, arterial blood was sampled and blood-gas tensions and serum $Na^+$ and $K^+$ concentrations were measured. If hypercarbia or hypoxia was present, it was corrected by increasing alveolar ventilation and inspiratory oxygen concentration. No abnormalities in serum $Na^+$ and $K^+$ concentrations were observed in any patient. Arterial blood-gas tensions and electrolyte balance, therefore, were within normal limits at the time that DL was given. No patient except one who had been prophylactically digitalized for paroxysmal tachycardia had received digitalis or $\beta$-adrenergic antagonists, and none had AV block before the DL administration. In two of the patients, PVCs were first treated with lidocaine before DL administration, but because the effects of lidocaine were either short or insufficient, PVCs reappeared shortly after the lidocaine treatment or were not eliminated by lidocaine. Blood pressure, heart rate, and ECG were recorded before and after the administration of DL.

The effects of DL on tachyarrhythmias associated with atrial fibrillation (AF) were examined in nine patients ranging in age from 34 to 81 yr, who had had AF preoperatively. DL was injected in bolus when tachycardia developed in response to AF during surgery. The initial dose of DL in all patients was 0.1 mg/kg. If the heart rate did not decrease to less than 100 beats/min, an additional dose ($\frac{1}{2}$–$\frac{2}{3}$ of the initial dose) was given 10–15 min after the first injection. Two of nine patients received an additional dose of 4 mg or 5 mg of DL. Four of the patients were under morphine–diazepam anesthesia for heart valve replacement, two were under enflurane anesthesia for abdominal surgery, two were under halothane anesthesia for vascular or gallbladder surgery, and one was under epidural anesthesia for inguinal hernioplasty. Seven of the patients had been digitalized preoperatively. None had received $\beta$-adrenergic antagonists or $Ca^{2+}$ antagonists. Blood pressure, heart rate, and ECG were recorded before the DL injection and at 5-min intervals for 30 min after.

Hemodynamic changes during the clinical study were expressed as means ± SEM and considered to be significant when *P* was less than 0.05 by paired *t*-tests.

## Results

### *Animal Study*

Arrhythmogenic doses of E during one MAC of halothane without DL averaged 1.13 ± 0.21 $\mu$g·kg$^{-1}$·min$^{-1}$. ADE increased significantly to 1.61 ± 0.33 and 3.14 ± 0.89 $\mu$g·kg$^{-1}$·min$^{-1}$ in the presence of 0.1 mg/kg and 0.3 mg/kg of DL, respectively (Fig. 1).

The P–Q interval 5 min after DL injection was prolonged from 94.3 ± 9.8 to 100.3 ± 9.4 msec by 0.1 mg/kg of DL ($P < 0.02$) and from 98.3 ± 11.2 to 110.5 ± 11.3 msec by 0.3 mg/kg of DL ($P < 0.01$).

Hemodynamic changes 5 min after the administration of DL are shown in Table 1. Systemic vascular and pulmonary vascular resistances were significantly

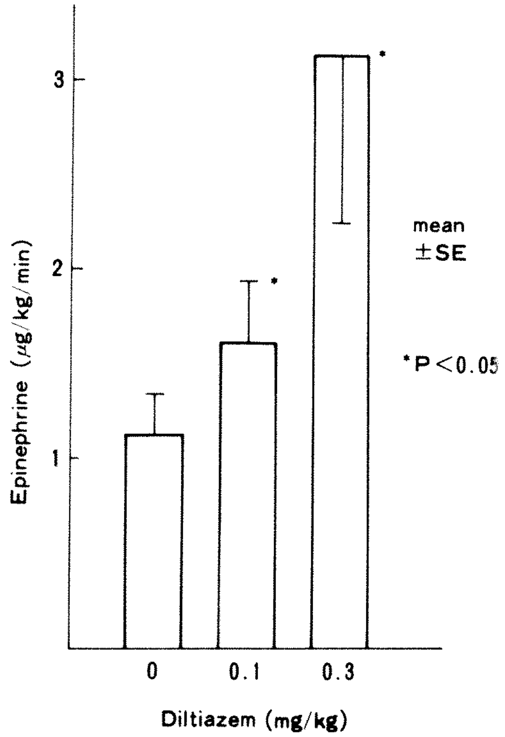


Figure 1. The effect of intravenous diltiazem upon the arrhythmogenic dose of epinephrine in dogs during one MAC halothane. $^*P < 0.05$ vs the values in the absence of diltiazem.

reduced. There was a slight but statistically significant increase in cardiac output. After the infusion of E systemic blood pressure (BP) increased for a few beats and then decreased for a few seconds before again increasing. BP reached its maximum height within 45 sec and remained stable during the E infusion. At the same infusion rate of E, BP was always higher in the absence of DL (the control) than in its presence. However, arrhythmias developed at the lower level of BP in the presence of DL than in its absence. For example, when arrhythmias developed, BP was 182.8 ± 16.2 mm Hg in the presence of 0.3 mg/kg of DL and 208.8 ± 17.4 mm Hg (±SEM) in the absence of DL. But the level of BP during ADE infusion, namely the level of BP when arrhythmias developed, tended to be lower than that during E infusion at a rate just one step lower than the ADE (at this level of BP arrhythmias were not observed) in the absence as well as in the presence of DL. This is because with ADE infusion, arrhythmias usually developed before the BP had reached its maximum, whereas with any infusion of E other than ADE, the BP reached its maximum. For example, in the presence of 0.3 mg/kg of DL, BP averaged 182.8 ± 16.2 mm Hg with the ADE and 187.0 ± 12.8 mm Hg with E infusion at the rate just one step lower than ADE.

Heart rate usually decreased after a transient increase during E infusion in the absence of DL and after 0.1 mg/kg of DL, but it increased during E infusion after 0.3 mg/kg of DL.

Table 1. Percentage Changes in Hemodynamic Function 5 min after the Intravenous Administration of Diltiazem to Dogs

| | Diltiazem | |
|---|---|---|
| | 0.1 mg/kg | 0.3 mg/kg |
| Mean BP<br>(100.5 ± 5.2 mm Hg) | 94.0 ± 1.4$^a$ | 93.8 ± 2.7 |
| Cardiac output<br>(2.02 ± 0.24 L/min) | 106.9 ± 1.8$^b$ | 107.4 ± 2.5$^b$ |
| SVR<br>(50.9 ± 5.2 RU) | 87.1 ± 2.3$^a$ | 87.0 ± 1.4$^c$ |
| PAP<br>(14.7 ± 0.2 mm Hg) | 100.1 ± 1.7 | 104.2 ± 1.7 |
| PVR<br>(4.1 ± 0.5 RU) | 89.0 ± 1.4$^c$ | 95.3 ± 1.4$^b$ |
| Heart rate<br>(119.7 ± 7.8 beats/min) | 98.4 ± 2.1 | 96.9 ± 1.9 |

Data in parentheses are mean ± SEM control data prior to injection of diltiazem. Figures not in parentheses are mean ± SEM percentages of control data. $^aP < 0.01$, $^bP < 0.05$, $^cP < 0.001$.

Abbreviations: BP, blood pressure; SVR, systemic vascular resistance; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; RU, mm Hg$^{-1}$·L$^{-1}$·min$^{-1}$.

## *Clinical Study*

*Effect on PVCs.* Ten patients were given DL, 0.1 mg/kg, intravenously intraoperatively as a bolus injection. Five patients had multifocal PVCs, and the other 5 had unifocal PVCs. All PVCs continued for more than 5 min before the injection of DL. When PVCs developed in nine of 10 patients, the blood pressure, heart rate, or both increased. These increases in blood pressure or heart rate seemed to be induced by surgical stimulation related to the start of surgery in five cases and by the intravenous administration of pancuronium in one case. In the remaining three cases no definite causes of these changes were found. In two of 10 cases, PVCs were first treated by lidocaine before DL was given; in one the lidocaine treatment was ineffective and in the other the duration of response to lidocaine was too brief to be effective even though lidocaine was injected twice.

In all 10 patients PVCs disappeared completely within 3.30 ± 0.62 min, but in one patient PVCs reappeared 10 min later. Figure 2 shows a typical case. Mean blood pressure decreased to 89.1 ± 2.4% of the control ($P < 0.01$) at 5 min and to 86.8 ± 2.2% ($P < 0.001$) at 30 min after the injection of DL. Heart rate gradually decreased to 94.8 ± 2.0% of the control ($P < 0.05$) at 5 min and to 87.5 ± 3.7% ($P < 0.01$) at 30 min after the DL injection.

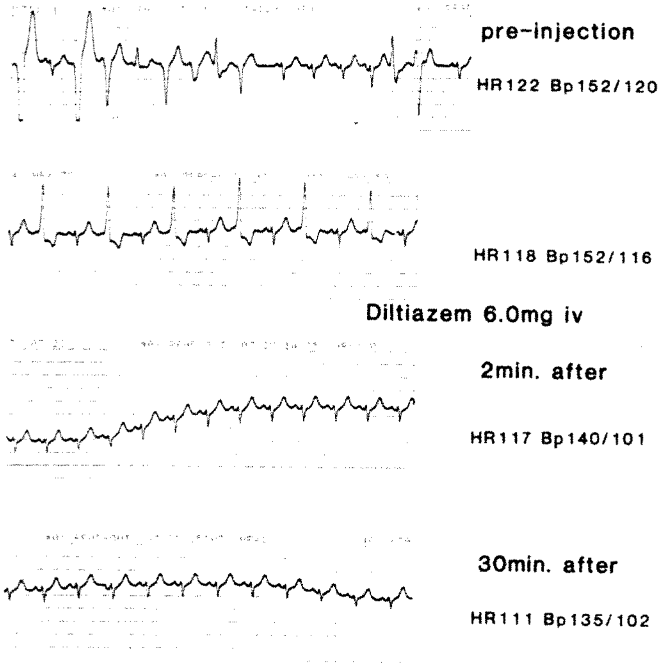


Figure 2. A representative case in which diltiazem effectively treated PVCs spontaneously appearing during halothane anesthesia. The patient, a 34-yr-old female, had onset of multifocal PVCs and bigeminy during operation for kidney stone. HR, heart rate; Bp, blood pressure.

*Effect on atrial fibrillation tachycardia.* Intravenous DL was given intraoperatively to nine patients who had had AF preoperatively and who developed tachyarrhythmias during anesthesia. Tachyarrhythmias developed when the tracheal intubation was performed in one case and when the operation was started in another case. In the other seven cases, tachyarrhythmias developed during the surgical operation, probably due to surgical stimulations. Tachyarrhythmias persisted about 10–15 min before DL was injected.

In all nine patients the heart rate was effectively reduced by DL to less than 100 beats/min. The maximum decrease in the heart rate was from 150 to 84, and the minimum was from 130 to 99. The decrease in the heart rate usually reached maximum about 15 min after injection of DL. Blood pressure decreased in five cases, remained unchanged in two, and increased in two. A typical case is illustrated in Figure 3.

## Discussion

### Animal Study

The present study demonstrates that DL increases the ADE during halothane anesthesia in the intact dog. This suggests that DL has an ability to increase the threshold level at which E produces arrhythmias during halothane anesthesia.

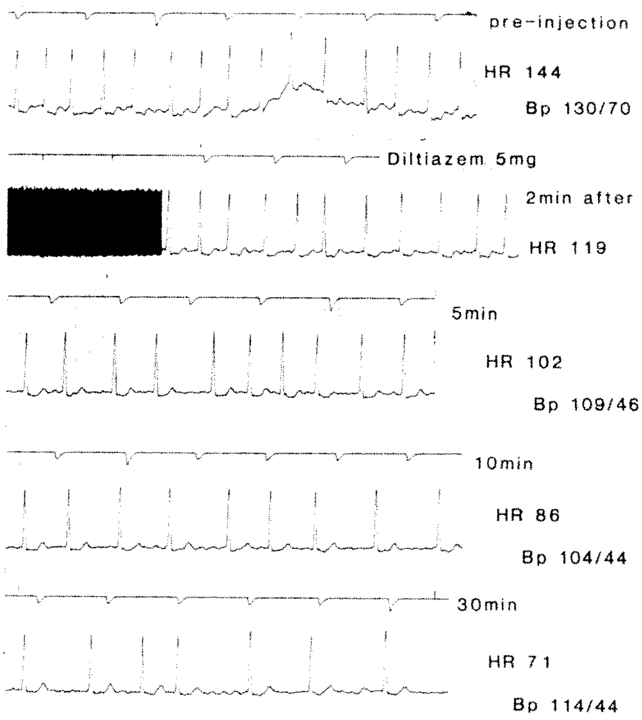

[redacted]

Figure 3. A representative case showing the effect of diltiazem upon atrial fibrillation (AF)-mediated tachyarrhythmia. The patient, 37-yr-old female with AF, was undergoing mitral and aortic valve replacement under morphine-$N_2O$ diazepam anesthesia. HR, heart rate; Bp, blood pressure.

The ADE during one MAC halothane in our study was less than that reported by Pace et al. (20), but corresponds to that reported by Munson and Tucker (21). The difference between our results and those of Pace et al. may result from the size of dogs, the nutritional state of dogs, and the depth of halothane anesthesia. Our dogs were small in size; and, because of malnutrition, the infusion of electrolyte–glucose solution was sometimes necessary and a metabolic acidosis had to be corrected by $NaHCO_3$ prior to the start of the study. The anesthetic level was lighter in our study.

The increase in BP caused by E is an important factor in the etiology of arrhythmias produced by E (22). If the antihypertensive effect of DL was the only cause of the antiarrhythmic effect of DL in this study, the BP measured in the absence of DL when arrhythmias developed by infusion of E should be the same or at least very close to the BP measured in the presence of DL. However, the BP level measured when arrhythmias were induced was significantly lower in the presence of DL than in its absence. Thus the antihypertensive action (i.e., an indirect effect) may play a part in the antiarrhythmic effect of DL in this study, but a direct antiarrhythmic effect might also contribute.

### *Clinical Study*

This is the first report to demonstrate the effectiveness of intravenous DL in the treatment of PVCs spontaneously occurring during halothane anesthesia. Moreover, this antiarrhythmic effect was effective on PVCs for which the treatment with lidocaine was insufficient or ineffective.

The major factors involved in the genesis of arrhythmias are abnormal impulse generation and an abnormal impulse conduction (23,24). There are two major types of abnormal impulse generation (24): enhanced automatic activity and triggered activity (i.e., the generation of one or more impulses as a consequence of a prior impulse). Both abnormal automatic and triggered activities are enhanced by increasing the extracellular $Ca^{2+}$ concentration, by catecholamines, and by digitalis overdose (24–26). Both activities are abolished by lowering extracellular $Ca^{2+}$, by exposure to $Mn^{2+}$, and by agents that block the slow inward $Ca^{2+}$ current (24–26). The slow inward $Ca^{2+}$ current, presumably moving through the slow channel, is thus important in the production of abnormal impulse generation.

Abnormal impulse conduction produces reentry types of arrhythmias because of unidirectional block and slow propagation of impulses brought about by depression of excitability of the conduction system or myocardial fibers. Such depression of excitability is mediated by partial depolarization of the resting membrane potential that suppresses the ability of the membrane to develop a normal rapid depolarization through $Na^+$ channels (i.e., the rapid response), so that only the ability of the membrane to undergo an active depolarization that conducts very slowly and that depends mainly on $Ca^{2+}$ to carry membrane current remains. This remaining ability, called the slow response, is enhanced by the addition of catecholamines (23,24). Hypoxia, poor perfusion, and ischemia are known to produce partial depolarization of cardiac fibers, not only by accelerating the slow responses due to the leak of $K^+$ from the intracellular to extracellular areas, but also by increasing the release of catecholamines (23,24). Accelerated slow responses, therefore, contribute greatly to the development of arrhythmias related to abnormal impulse conduction.

Because the electrophysiologic function of ventricular muscle is dominated by a fast channel, the effectiveness of a slow channel inhibitor in the treatment of ventricular dysrhythmias has been doubted. However, as discussed above, enhanced or activated slow responses are responsible for the two major factors involved in the production of arrhythmias, abnormal impulse generation, and conduction. The use of slow channel inhibitors in the treatment of certain types of arrhythmias is, therefore, theoretically reasonable. Antiarrhythmic effects of DL on oubain- and epinephrine-induced arrhythmia as well as on ischemia-mediated fibrillation and reentrant ventricular arrhythmia have been reported in animal experiments (13,14,16,27).

In addition to its effect on slow channels, DL improves the relationship between myocardial $O_2$ supply and demand by increasing coronary and collateral blood flow and by decreasing $O_2$ consumption as a result of reductions in afterload, heart rate, and contractility (6–9). DL also possesses a nonspecific antiadrenergic effect (7,9,28). These two effects also may contribute to the antiarrhythmic effect of DL, especially if arrhythmias are associated with myocardial ischemia or sympathetic hyperactivity.

The causes for PVCs observed in this study are difficult to define. However, hypoxia, hypercarbia, and serum $Na^+$ and $K^+$ abnormality (each of which can cause arrhythmias) are ruled out. Hypertension and tachycardia, both of which accompanied PVCs in our study, may have been causative factors in the PVCs. Hypertension and tachycardia, the result of increased sympathetic activity associated with surgical procedures, may produce an imbalance in the relation between myocardial $O_2$ supply and demand second to increased $O_2$ requirements. DL may act to improve these conditions, thus producing its antiarrhythmic effects on PVCs in addition to its direct effects on slow channels.

Verapamil, another slow channel inhibitor, is also useful in the treatment of PVCs during anesthesia (29). The effect of intravenous DL in management of acute PVCs stands in contrast to its lack of comparable efficacy in the management of patients with chronic PVCs (30).

Suddenly developing tachyarrhythmias associated with AF during anesthesia were also effectively treated by the intravenous injection of DL in the present study. The heart rate was reduced from approximately 140 beats/min to less than 100 beats/min within 10–15 min after intravenous DL.

Because the dominant function of the atrioventricular node depends on slow channels (9), and since a slow channel inhibitor prolongs AV conduction and the AV nodal refractory period (5,9,31), it is possible to predict the efficiency of a slow channel inhibitor in reducing a ventricular rate increased by AF. In fact, verapamil reduced the heart rate in 98.5% of the patients during AF, including 5.5% of the patients in which AF was converted to sinus rhythm (31). Even after open-heart surgery, verapamil was 100% successful in treatment of AF-mediated tachyarrhythmias (32,33).

The effect of DL on AF-mediated tachyarrhythmias, however, has been reported only in a limited series of cases: 12 cases by Oyama (34), two cases by Rozanski et al. (17), four by Sugimoto et al. (35), and 12 by Betriu et al. (18), plus our nine present cases. In 37 of these 39 cases, DL reduced the heart rate to less than 100 beats/min, and in two of these cases AF was converted to sinus rhythm (18). DL and verapamil, therefore, might be the drugs of choice for reducing the ventricular response to AF and for slowing the heart rate, although conversion of AF to sinus rhythm is infrequent.

Pharmacologic effects of DL on the sinus and AV nodes and on the coronary circulation are similar to those of verapamil (5,9), and the antiarrhythmic effect of DL, as discussed above, also seems to resemble that of verapamil. However, DL has, a weaker negative inotropic effect than verapamil, a stronger inhibitory effect on spontaneous atrial rate (8,36), a less pronounced reflex-mediated positive chronotropic effect (5,7,37), and a greater nonspecific sympathetic inhibitory effect. Therefore, the advantage of DL over verapamil may be its effect in management of arrhythmias associated with hypertension and tachycardia secondary to increased sympathetic activity. The other slow channel inhibitors, nifedipine and nicardipine, do not have antiarrhythmic effects (7,28,36).

One of the advantages of a slow channel inhibitor over other antiarrhythmic agents is that the duration of action is longer than it is with drugs such as lidocaine (7,36). In this study there was one patient in whom repeated injections of lidocaine at 10–15-min intervals failed to affect the PVCs, which were then completely abolished by a single injection of DL. The bronchodilating property of slow channel inhibitors may also represent an advantage over $\beta$-adrenergic antagonists (38,39). In patients with bronchial asthma or chronic obstructive lung disease, slow channel inhibitors may be the drugs of choice.

One disadvantage of DL and other slow channel inhibitors is the circulatory depression, namely the reduction of blood pressure and the depression of myocardial contractility that they produce. These effects were, however, mild and not clinically significant in the doses used for the treatment of arrhythmias. Moreover, the decrease in blood pressure produced by DL is associated with an increase in cardiac output (34,40,41), even under halothane anesthesia (42), probably due to the reduction of ventricular afterload. The only major disadvantage of DL is its ability to prolong AV conduction and depress the sinus node (5,9,31). Therefore, use of DL in patients with AV block or sick sinus is not recommended, and DL in combination with drugs that prolong AV conduction and depress sinus node function, such as digitalis and $\beta$-adrenergic antagonists, should be used with caution. In our cases, circulatory depressant effects were not observed when DL was used in fully digitalized patients.

In conclusion, our data in animals showing that DL increases the ADE during halothane anesthesia suggest that DL may be useful as an antiarrhythmic agent in the management of E-related arrhythmias. Our data in patients in whom PVCs developed during halothane anesthesia show that intravenous DL is an effective means for treatment of such PVCs. Tachyarrhythmias mediated by AF were also effectively treated by bolus injection of DL. DL is recommended as an antiarrhythmic agent during anesthesia for acute onset of PVCs and tachyarrhythmias mediated by AF.

## References

1. Nakajima H, Hoshiyama M, Yamashita K, Kiyomoto A. Effect of diltiazem on electrical and mechanical activity of isolated cardiac ventricular muscle of guinea pig. Jpn J Pharmacol 1975;25:383–92.
2. Himori N, Ono H, Taira N. Simultaneous assessment of effects of coronary vasodilators on the coronary blood flow and the myocardial contractility by using the blood-perfused canine papillary muscle. Jpn J Pharmacol 1976;26:427–35.
3. Nabata H. Effect of calcium-antagonistic coronary vasodilators on myocardial contractility and membrane potentials. Jpn J Pharmacol 1977;27:239–49.
4. van Breemen C, Hwang O, Meisheri KD. The mechanism of inhibitory action of diltiazem on vascular smooth muscle contractility. J Pharmacol Exp Ther 1981;218:459–63.
5. Mitchell LB, Schroeder JS, Mason JW. Comparative clinical electrophysiologic effects of diltiazem, verapamil and nifedipine: a review. Am J Cardiol 1982;49:629–35.
6. McAuley BJ, Schroeder JS. The use of diltiazem hydrochloride in cardiovascular disorders. Pharmacotherapy 1982;2:121–33.
7. Ellrodt G, Chew CYC, Singh BN. Therapeutic implication of slow-channel blockade in cardiocirculatory disorders. Circulation 1980;62:660–79.
8. Stone PH, Antman EM, Muller JE, Braunwald E. Calcium channel blocking agents in the treatment of cardiovascular disorders. Part II: Hemodynamic effects and clinical applications. Ann Intern Med 1980;93:886–904.
9. Singh BN. Pharmacological basis for the therapeutic application of slow-channel blocking drugs. Angiology 1982;33:492–515.
10. McGraw BF, Walker SD, Hemberger JA, Gitomer SL, Nakama M. Clinical experience with diltiazem in Japan. Pharmacotherapy 1982;2:151–61.
11. McAllister RG Jr. Clinical pharmacology of slow channel blocking agents. Prog Cardiovasc Dis 1982;25:83–102.
12. Saikawa T, Nagamoto Y, Arita M. Electrophysiologic effects of diltiazem, a new slow channel inhibitor, on canine cardiac fibers. Jpn Heart J 1977;18:235–45.
13. Yamada K, Shimamura T, Nakajima H. Study on a new 1,5-benzothiazepine derivative (CRD-401). V. Antiarrhythmic actions. Jpn J Pharmacol 1973;23:321–8.

14. Clusin WT, Bristow MR, Baim DS, et al. The effects of diltiazem and reduced serum ionized calcium on ischemic ventricular fibrillation in the dog. Circ Res 1982;50:518–26.

15. Sheehan FH, Epstein SE. Effects of calcium channel blocking agents on reperfusion arrhythmias. Am Heart J 1982;103:973–7.

16. Peter T, Fujimoto T, Hamamoto H, McCullen A, Mandel EJ. Electrophysiologic effects of diltiazem in canine myocardium, with special reference to conduction delay during ischemia. Am J Cardiol 1982;49:602–5.

17. Rozanski JJ, Zaman L, Castellanos A. Electrophysiologic effects of diltiazem hydrochloride in supraventricular tachycardia. Am J Cardiol 1982;49:621–8.

18. Betriu A, Chaitman BR, Bourassa MG, et al. Beneficial effect of intravenous diltiazem in the acute management of paroxysmal supraventricular tachyarrhythmias. Circulation 1983;67:88–94.

19. Yen S, Kou H, Lin F, Hung J, Wu D. Effects of oral diltiazem in paroxysmal supraventricular tachycardia. Am J Cardiol 1983;52:271–8.

20. Pace NL, Ohmura A, Wong KC. Epinephrine-induced arrhythmias: effect of exogenous prostaglandins and prostaglandin synthesis inhibitor during halothane anesthesia in the dog. Anesth Analg 1979;58:401–4.

21. Munson ES, Tucker WK. Doses of epinephrine causing arrhythmia during enflurane, methoxyflurane and halothane anaesthesia in dogs. Can Anaesth Soc J 1975;22:495–501.

22. Katz RL, Epstein RA. The interaction of anesthetic agents and adrenergic drugs to produce cardiac arrhythmias. Anesthesiology 1968;29:763–84.

23. Cranefield PF, Wit AL, Hoffman BF. Genesis of cardiac arrhythmias. Circulation 1973;47:190–204.

24. Hoffman BF, Rosen MR. Cellular mechanisms for cardiac arrhythmias. Circ Res 1981;49:1–15.

25. Imanishi S, Surawicz B. Automatic activity in depolarized guinea pig ventricular myocardium. Characteristics and mechanisms. Circ Res 1976;39:751–9.

26. Cranefield PF. Action potentials, afterpotentials, and arrhythmias. Circ Res 1977;41:415–23.

27. Fujimoto T, Peter T, Hamamoto H, Mandel EJ. Effects of diltiazem on conduction of premature impulses during acute myocardial ischemia and reperfusion. Am J Cardiol 1981;48:851–7.

28. Singh BN, Nademanee K, Baky SH. Calcium antagonists. Clinical use in the treatment of arrhythmias. Drugs 1983;25:125–53.

29. Brichard G, Zimmerman P. Verapamil in cardiac dysrhythmias during anaesthesia. Br J Anaesth 1970;42:1005–11.

30. Mitsuoka T, Yano T, Matsumoto Y, Kitani F, Fukaya M, Hashiba Y. Effect of intravenous diltiazem on cardiac arrhythmias (in Japanese). Jpn Pharmacol Ther 1983;11(suppl 1):147–9.

31. Talano JV, Tommaso C. Slow channel calcium antagonists in the treatment of supraventricular tachycardia. Prog Cardiovasc Dis 1982;25:141–56.

32. Gray RJ, Conklin CM, Sethna DH, Mandel WJ, Matloff JM. Role of intravenous verapamil in supraventricular tachyarrhythmias after open-heart surgery. Am Heart J 1982;104:799–802.

33. Plum VJ, Karp RB, Kouchouks NT, Zorn GL Jr, James TN, Waldo AL. Verapamil therapy of atrial fibrillation and atrial flutter following cardiac operation. J Thorac Cardiovasc Surg 1982;83:590–6.

34. Oyama Y. Hemodynamics and electrophysiological evaluations of diltiazem hydrochloride: a clinical study. In: Bing RJ, eds. New drug therapy with a calcium antagonist. Diltiazem Hakone Symposium '78. Amsterdam: Exerpta Medica, 1979:169–89.

35. Sugimoto T, Uraoka T, Terada Y, et al. Oral and intravenous administration of diltiazem in the management of various kinds of arrhythmias (in Japanese). Jpn Pharmacol Ther 1982;10(suppl 2):153–64.

36. Henry PD. Comparative pharmacology of calcium antagonists: nifedipine, verapamil and diltiazem. Am J Cardiol 1980;46:1047–58.

37. Nakaya H, Schwartz A, Millard RW. Reflex chronotropic and inotropic effects of calcium channel-blocking agents in conscious dogs. Diltiazem, verapamil, and nifedipine compared. Circ Res 1983;52:302–11.

38. Farly JM, Miles PR. The sources of calcium for acetylcholine-induced contractions of dog tracheal smooth muscle. J Pharmacol Exp Ther 1978;207:340–6.

39. Patel KR. Calcium antagonists in exercise-induced asthma. Br Med J 1981;282:932–3.

40. Nishimura N, Mori Y, Kusumoto H, Kamekawa R, Ino A, Metori S. Clinical studies on anesthesia adjutants. 2. Circulatory effects of CRD-401. (In Japanese with abstract in English.) Jpn J Anesthesiol 1972;21:1147–51.

41. Tubau JF, Cote P, Bourassa MG. Systemic and coronary hemodynamics of intravenous diltiazem in patients with coronary artery disease. Am J Cardiol 1980;45:439.

42. Iwatsuki N, Amaha K, Koga Y, Hoshi Y, Obara S. Interaction between diltiazem and halothane upon canine cardiovascular hemodynamics. (In Japanese with abstract in English.) Jpn J Anesthesiology 1984;33:1196–1203.

# Inhibition of Postoperative Pain by Continuous Low-Dose Intravenous Infusion of Lidocaine

Jean Cassuto, MD, PhD, Gunnar Wallin, MD, Seth Högström, MD, Anders Faxén, MD, PhD, and Gunnar Rimbäck, MD

CASSUTO J, WALLIN G, HÖGSTRÖM S, FAXÉN A, RIMBÄCK G. Inhibition of postoperative pain by continuous low-dose intravenous infusion of lidocaine. Anesth Analg 1985;64:971–4.

*Intravenous lidocaine has been reported previously to inhibit postoperative pain when given either as single injections or as short infusions in amounts usually causing adverse reactions. To determine the efficacy of a continuous low-dose (2 mg/kg) intravenous infusion of lidocaine, postoperative pain (visual analogue pain scale) and the requirements for postoperative analgesics were measured in a double-blind randomized trial in 20 patients after cholecystectomy. Lidocaine infusion was started 30 min before the operation and continued for 24 hr after surgery ($n = 10$). Saline was infused in a comparable group of ten patients. The lidocaine-treated patients had significantly lower pain scores during the first day after surgery ($P < 0.001$) and required significantly less meperidine during the first ($P < 0.02$) and second postoperative days ($P < 0.01$). No adverse reactions to lidocaine were observed. Whole blood levels of lidocaine ranged between 1 and 2 μg/ml. The results suggest that low-dose continuous infusions of lidocaine decrease the severity of postoperative pain and are devoid of side effects.*

Key Words: ANESTHETICS, LOCAL—lidocaine. PAIN—postoperative.

Operations in the upper abdomen often are associated with particularly severe postoperative pain (1). Furthermore, ventilation is often inhibited by the pain. To relieve the pain, potent narcotics have to be used, which leads to a more pronounced respiratory depression (2). It is, therefore, desirable to reduce the need for narcotic analgesics in the postoperative period.

Intravenous lidocaine has been shown previously to relieve cancer pain (3), chronic pain (4,5), pain due to adiposis dolorosa (6,7), and pain after surgery (8,9). In the last two studies, single injections or short infusions of lidocaine restricted to the time of surgery were administered in doses great enough to increase the risk of toxic side effects. To minimize adverse reactions, we gave lidocaine as a continuous low-dose intravenous infusion and evaluated its postoperative analgesic effect.

## Methods

Twenty patients (12 women, 8 men) scheduled for elective cholecystectomy were studied. Each patient gave his or her informed consent to inclusion in the study and the experimental protocol was approved by the Regional Ethical Committee. Patients with hepatic, renal, or cardiovascular disease were excluded. Preanesthetic medication consisted of 0.05–0.075 mg fentanyl and 2.50–3.75 mg droperidol intramuscularly. Anesthesia was induced with thiopental (4 mg/kg). After the administration of 1 mg of pancuronium to prevent fasciculations, endotracheal intubation was performed with the aid of succinylcholine (1 mg/kg). After intubation, 5 mg of pancuronium was given with additional doses of 1 mg as indicated during surgery. Anesthesia was maintained with $N_2O$ and $O_2$ and a standardized dose of $0.003\ \text{mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ of fentanyl. At the conclusion of surgery, 0.5 mg of atropine followed by 1 mg of neostigmine was administered to reverse neuromuscular blockade.

Half an hour before skin incision, one group of patients ($n = 10$) received an intravenous bolus injection of lidocaine (100 mg; 20 mg/ml) followed by an intravenous infusion at 2 mg/min (2 g lidocaine in 500 ml physiologic saline) that was continued until the twenty-fourth postoperative hour. A placebo group ($n = 10$) received an infusion of saline. Patients were monitored by measurements of systolic blood pressure and pulse rate as well as by continuous monitoring of the ECG (alarm with automatic registration on paper was set for irregular heart beats and heart

---

This study was supported by grants from the Medical Society of Göteborg. Received from the Departments of Anesthesiology and Surgery, Central Hospital, Mölndal, Sweden. Accepted for publication April 12, 1985.

Address correspondence to Dr. Cassuto, Department of Anesthesiology, Central Hospital, S-431 80 Mölndal, Sweden.

© 1985 by the International Anesthesia Research Society

rate beyond 50–100 beats/min), throughout the period of lidocaine/saline infusion.

A questionnaire concerning postoperative nausea, vomiting, and adverse reactions to lidocaine (lightheadedness, tinnitus, perioral numbness, drowsiness, and slurred speech) was filled out by the patients on the morning of the first postoperative day.

### *Blood Concentrations of Lidocaine*

Lidocaine concentrations in whole blood from eight patients were determined at Astra Läkemedel AB, Research and Development Laboratories, Södertälje, Sweden by mass fragmentography (10). Venous blood samples (5 ml) were drawn from a peripheral vein in heparinized tubes 8 hr and 20 hr after the start of the lidocaine infusion and kept frozen at −20°C until analysis. Whole blood levels of lidocaine are expressed as $\mu$g lidocaine base/ml whole blood.

### *Pain Assessment*

Pain during the initial 24 hr after surgery was assessed using a linear analogue scale ranging from 0 (no pain) to 100 (pain as bad as it could be) (11). Each patient scored his pain at 2-hr intervals, starting 1 hr after the return from the operating room (at which point all the patients had recovered consciousness). No meperidine was administered before the first pain assessment. When patients complained of pain they were given injections of 50 mg of meperidine intramuscularly until pain was relieved. Each patient's requirements for meperidine were recorded for 48 hr after surgery.

The study was double-blind randomized. Standard $t$-tests were used to calculate significant differences between means and accumulated pain scores (the total pain scores during 24 hr were calculated for each patient and the difference between the two groups was analyzed). Data are expressed as mean ± SEM.

## Results

The two groups of patients were comparable with regard to age, weight, distribution of sex, and the duration of surgery (Table 1). Pain scores were reduced significantly in the lidocaine-treated patients ($P < 0.001$) at the first pain assessment 1 hr after the return from the operating room, i.e., before any of the patients had been given meperidine. The estimated mean of the accumulated pain scores was significantly higher in the control group (29.3 ± 2.5) than in the lidocaine-treated group (9.4 ± 2.0) ($P < 0.001$) (Fig. 1). Furthermore, intravenous lidocaine significantly reduced the need for meperidine during the first ($P < 0.02$) and second postoperative day ($P < 0.01$) (Fig. 2).

Table 1. Clinical Data in Patients

| | Lidocaine intravenously ($n$ = 10) | Saline intravenously ($n$ = 10) |
|---|---|---|
| Age (yr) | 44 (30–67)$^a$ | 55 (34–68) |
| Weight (kg) | 72 (54–93) | 70 (55–105) |
| Sex (female/male) | 4/6 | 5/5 |
| Duration of surgery (min) | 105 (75–150) | 112 (68–150) |
| Nausea | 6$^b$ | 8 |
| Vomiting | 5 | 4 |

$^a$Median and range.
$^b$Number of patients.

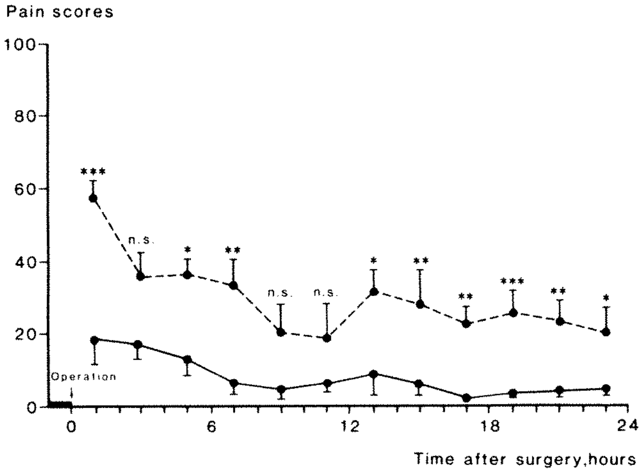


Figure 1. Pain scores during the initial 24 hr after surgery in lidocaine-treated patients (—) and in control patients (---). Differences are calculated between means using two-tailed Student's $t$-test. Accumulated pain scores were significantly lower in the lidocaine-treated group as compared to control ($P < 0.001$). Symbols: NS, not significant; $^*P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ compared with control data. Data were expressed as mean ± SEM.

Systolic blood pressure and pulse rate did not differ significantly in the two groups of patients, and no ECG abnormalities were reported. Aside from lightheadedness reported by one patient in each group, no subjective side effects due to possible drug overdose were reported. The incidence of postoperative nausea and vomiting did not differ significantly in the two groups (Table 1). Whole blood levels of lidocaine 8 hr after the start of infusion averaged 1.52 ± 0.29 $\mu$g/ml and at 20 hr 1.75 ± 0.34 $\mu$g/ml.

## Discussion

Our results show a significant reduction in the need for meperidine during the first and second postop-

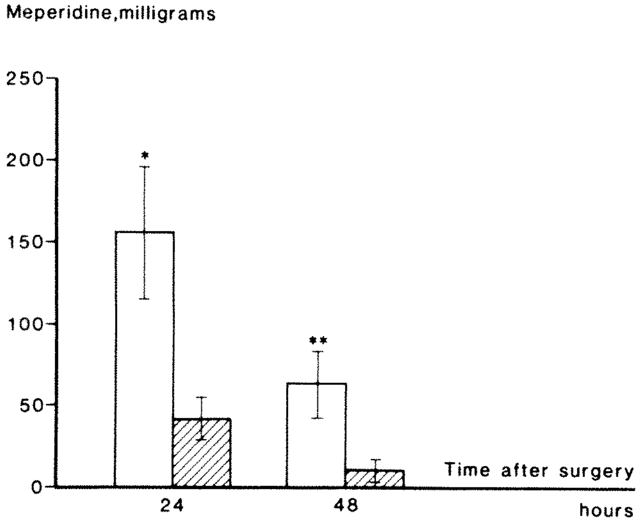


Figure 2. Meperidine requirements during the first and second postoperative days in patients receiving intravenous lidocaine (shaded bars) and in control patients (open bars). Symbols: $^*P < 0.02$; $^{**}P < 0.01$ compared with control data. Data are expressed as mean ± SEM.

erative days after cholecystectomy in patients given low-dose 24-hr infusion of lidocaine. Previous authors (9) have reported a significant analgesic effect of intravenous lidocaine extending into the third postoperative day after 1000 mg of lidocaine was given during the operation. A long-lasting effect was also present in our study, as judged by the significantly reduced need for meperidine during the second postoperative day (Fig. 2). The analgesic effect of lidocaine during the 24–48 hr period after surgery may reflect the fact that adequate blood levels of lidocaine were still present during that time, as has been shown in cardiac patients after 24–48 hr of lidocaine infusion (12). Our data also demonstrate a significantly lower pain score in the lidocaine-treated patients (Fig. 1) despite the fact that patients given placebo infusion received significantly higher doses of meperidine (Fig. 2). This analgesic effect of lidocaine was apparent as soon as 1 hr after the end of the operation as judged by the difference in pain score before any of the patients had meperidine (Fig. 1). There could be several mechanisms for this rather potent analgesic effect: intravenous infusions of lidocaine have been shown to induce sedation in animals (13,14) and humans (15,16), implying a central site of action and an anesthetic, rather than analgesic, effect; sedation and other subjective side effects in humans have been reported at infusion rates of 7.5–12.5 mg/min (15) and 500 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (14), which is substantially higher than the infusion rate used in this study (2 mg/min corresponding to 29 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in a 70-kg patient). Pain impulses from the operative area are carried to the central nervous system by afferent A-delta and C-fibers (17). Thorén and Öberg (18) have shown that intravenous infusion of lidocaine at infusion rates similar to ours markedly attenuated activity in cardiac C-fibers after cardiac ischemia, results suggesting a peripheral analgesic effect for low-dose lidocaine, although a dual, i.e., peripheral and central effect cannot be ruled out.

The infusion rate of lidocaine used in this study produced a whole blood concentration of 1–2 μg/ml. This dose did not cause toxic side effects or significant changes in pulse rate or systolic blood pressure. These observations are in accordance with previous observations that lidocaine administered in the same amounts as in this study does not induce cardiovascular effects (19).

Our results suggest that low-dose continuous infusion of lidocaine is devoid of side effects and can be used to decrease the severity of postoperative pain, thus reducing the need for potent morphinomimetic drugs in the postoperative period.

## References

1. Parkhouse J, Lambrechts W, Simpson BRJ. The incidence of postoperative pain. Br J Anaesth 1961;33:345–53.
2. Jaffe JH, Martin WR. Opioid analgesics and antagonists. In: Goodman LS, Gilman A, eds. The pharmacological basis of therapeutics. 6th ed. New York: Macmillan 1980;494–534.
3. Gilbert CRA, Hanson IR, Brown AB, Hingson RA. Intravenous use of xylocaine. Anesth Analg 1951;30:301–13.
4. Boas RA, Covino BG, Shahnarian A. Analgesic responses to i.v. lignocaine. Br J Anaesth 1982;54:501–5.
5. Edwards WT, Barney RG, Habib F. Intravenous lidocaine in chronic pain—three years experience. Regional Anesth 1984;9:48.
6. Iwane T, Maruyama M, Matsuki M, Ito Y, Shimoji K. Management of intractable pain in adiposis dolorosa with intravenous administration of lidocaine. Anesth Analg 1976;55:257–9.
7. Atkinson RL. Intravenous lidocaine for the treatment of intractable pain of adiposis dolorosa. Int J Obesity 1982;56:351–7.
8. DeClive-Lowe SG, Desmond J, North J. Intravenous lignocaine anaesthesia. Anaesthesia 1958;13:138–46.
9. Bartlett EE, Hutaserani O. Xylocaine for the relief of postoperative pain. Anesth Analg 1961;40:296–304.
10. Hignite CE, Tschanz CH, Steiner J, Huffman DH, Azarnoff DL. Quantitation of lidocaine and its de-ethylated metabolites in plasma and urine by gas chromatography—mass fragmentography. J Chromatogr 1978;161:243–9.
11. Revill SI, Robinson JO, Rosen M, Hogg MI. The reliability of a linear analogue for evaluating pain. Anaesthesia 1976;31:1191–8.
12. Prescott LF, Nimmo J. Plasma lidocaine concentrations during and after prolonged infusions in patients with myocardial infarction. In: Scott DB, Julian DG, eds. E & S Livingston, Edinburgh and London, 1971.
13. Wagman IH, de Jong RH, Prince DA. Effects of lidocaine on the central nervous system. Anesthesiology 1967;28:155–72.
14. Sakabe T, Mackawa T, Ishikawa T, Takeshita H. The effects of

lidocaine on canine cerebral metabolism and circulation related to the electroencephalogram. Anesthesiology 1974;40:433–41.

15. Foldes FF, Molloy R, McNall PG, Koukal LR. Comparison of toxicity of intravenously given local anesthetic agents in man. JAMA 1960;172:1493–8.
16. Koppanyi T. The sedative central analgesic and anticonvulsant actions of local anesthetics. Am J Med Sci 1962;244:646–54.
17. Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965;150:971–9.
18. Thorén P, Öberg B. Studies on the endoanesthetic effects of lidocaine and benzonatate on non-medullated nerve endings in the left ventricle. Acta Physiol Scand 1981;11:51–8.
19. Covino BG, Vassallo HG. Local anesthetics, mechanisms of action and clinical use. New York: Grune & Stratton 1976:131–40.

ANESTH ANALG
1985;64:975–80

# Modulation of a GABA-Ergic Inhibitory Circuit in the In Vitro Hippocampus by Etomidate Isomers

David Ashton, PhD, and Albert Wauquier, PhD

ASHTON D, WAUQUIER A. Modulation of a GABA-ergic inhibitory circuit in the in vitro hippocampus by etomidate isomers. Anesth Analg 1985;64:975–80.

*A pulse-paired stimulation technique was used to examine the in vitro effects of the isomers of etomidate on synaptic transmission between Schaffer collaterals and $CA_1$ pyramidal cells in the guinea pig hippocampus. Etomidate produced a dose-related, stereospecific, reversible increase in paired-pulse inhibition. Replacement of Cl by isethionate reversed the inhibition induced by (+)-etomidate. Together with earlier biochemical evidence, these results show that in the mammalian CNS (+)-etomidate enhances central inhibition by increasing the effectiveness of γ-aminobutyric acid (GABA) in a chloride-dependent fashion.*

Key Words: ANESTHETICS, INTRAVENOUS—etomidate.

Etomidate is a short-acting nonbarbiturate hypnotic devoid of analgesic properties (1). Etomidate also shows potent anticonvulsant activity in various animal tests including the maximal metrazol test (2), the D,L-allylglycine seizure test (3), the bicuculline-seizure threshold test (4), and amygdaloid kindled seizures (5,6). In humans, etomidate has been used successfully to terminate therapy-resistant status epilepticus (7,8). Etomidate has two optical isomers, the (+) isomer being the active one for the hypnotic and anticonvulsant action (1,9).

In in vitro receptor binding assays in which (+)-etomidate was shown to enhance $^3$H-diazepam binding to rat forebrain, (−)-etomidate was inactive (10). The enhancement of $^3$H-diazepam binding by (+)-etomidate was due to an increase in binding affinity, the maximal number of sites remained unchanged (10). (+)-Etomidate did not inhibit $^3$H-muscimol binding to GABA-receptors, nor did it displace $^3$H-flunitrazepam or inhibit other receptor binding assays (10). These observations led to the suggestion that (+)-etomidate binds to the chloride-ionophore of the γ-aminobutyric acid (GABA)-receptor complex in such a way as to increase the efficacy of GABA-ergic neuronal inhibition (10). Further biochemical (11) and in vivo pharmacological data (4) have been produced that support this hypothesis.

Figure 1 diagrammatically shows the local neuronal circuits in area $CA_1$ of the hippocampus. The afferent axons making synaptic contact with pyramidal cells (P) are called Schaffer collaterals. The prominent inhibitory postsynaptic potential (IPSP) that can be recorded intracellularly from hippocampal pyramidal cells (12–14) can be accounted for largely by a pyramidal cell axon collateral system that activates basket-cells (Fig. 1,(i)) to recurrently inhibit the pyramidal cell body via release of GABA (15–17). This inhibitory feedback loop can be activated using a paired-pulse stimulation technique (18,19). The first stimulation pulse or conditioning pulse produces an evoked response and activates the inhibitory circuit; if the second pulse or test pulse then decreases during the time course of the inhibition, the test pulse produces a smaller evoked response. The strength of the inhibitory response can be judged by comparing the magnitude of the evoked response generated by the test and conditioning pulse. We have used this technique in our study to examine the action of the isomers of etomidate in the in vitro hippocampal slice preparation. The preparation offers several advantages for the evaluation of the CNS effects of anesthetic agents, including the absence of basal anesthesia and associated cardiovascular changes. In addition, the lamellar organization of neurons in the transverse hippocampal slice allows visualization of the cell body layer for the placement of electrodes.

---

This study was funded in part with a grant from the IWONL (Belgium). Received from the Department of Neuropharmacology, Janssen Pharmaceutica, Beerse, Belgium. Accepted for publication April 29, 1985.

Address correspondence to Dr. Ashton, Department of Neuropharmacology, Janssen Pharmaceutica, Turnhoutseweg 30, 2340 Beerse, Belgium.

© 1985 by the International Anesthesia Research Society

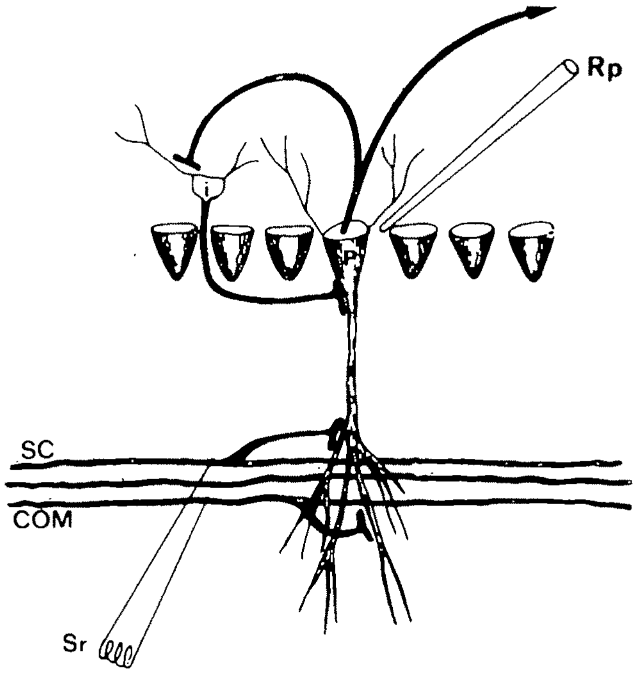


Figure 1. Diagram of local neuronal circuit in area. $CA_1$ of the hippocampal slice. P is a pyramidal neuron. SC are Schaffer collaterals coming from $CA_3$ that synapse with pyramidal cell dendrites. The pyramidal cell axon has a collateral that makes synaptic contact with a basket cell (i). The basket cells (i) release GABA as their neurotransmitter at synapses on the pyramidal neuron's cell body. Rp is a glass extracellular recording electrode placed among $CA_1$ pyramidal cells. Sr is a bipolar stimulating electrode placed on the Schaffer collaterals.

## Methods

400-μm thick transverse hippocampal slices were prepared from male 300–400 g guinea pigs using normal techniques (20). The slices were placed on a gold grid at the interface between humidified 95% $O_2$/5% $CO_2$ and oxygenated artificial cerebrospinal fluid (ACSF) in a laminar flow chamber. ACSF was composed of NaCl, 134 mM; KCl, 4 mM; $KH_2PO_4$, 1.25 mM; $NaHCO_3$, 22 mM; $CaCl_2$, 2 mM; $MgSO_4$, 1.1. mM; and D-glucose, 10 mM. Chamber temperature was 30°C. The ACSF flow rate was 3 ml/min.

After a 1-hr recovery period, a bipolar stimulating electrode was placed on the Schaffer collaterals (Fig. 1 (Sr)) for orthodromic activation. A glass recording electrode filled with 2 M NaCl (resistance 1–5 M Ω) was placed among the cell bodies of pyramidal neurons in the $CA_1$ area of the hippocampus (Fig. 1 (Rp)). Stimulation of Schaffer collaterals produced a typical evoked response at the $CA_1$ cell body layer. The evoked potential consisted of a slow positive wave (field EPSP) interrupted by a fast negativity (population spike) (see Fig. 3(*A*)). The population spike is the extracellularly recorded action potential of groups of pyramidal neurons (21). The population spike amplitude was defined as the number of mV between the most negative peak and the mean value of the preceding and following positive deflections of the field EPSP.

Evoked potentials were passed via a WPI gold probe to a WPI KS700 electrometer, displayed on a Tectronix oscilloscope, passed to an A/D converter, digitized at a rate of 6.5 kHz, and stored and analyzed by a HP 9816 computer. The computer automatically calculated the field EPSP latency, field EPSP slope, population spike latency, population spike amplitude and DC potential of each evoked response.

Plots of population spike amplitude vs stimulation voltage (input/output curves) were generated automatically by the computer with an interstimulation frequency of 0.1 Hz and voltage between 4 and 12 V. These curves allowed determination of population spike threshold and maximal population spike amplitude. Population spike threshold was defined as that stimulation voltage producing a $>$ 0.2 mV population spike in 2 out of 3 stimulations. Maximal population spike amplitude was the maximal amplitude of the population spike during the input/output curve.

### *Experimental Procedures*

After placing the stimulation and recording electrodes, initial stimulation variables were set such that an evoked response was produced with a population spike amplitude in excess of 4 mV. Slices were stimulated with 100–200 μsec pulses at a voltage between 4 and 12 V and at a frequency of 0.05 Hz. The frequency of stimulation was increased to 0.1 Hz during input/output curves. Once set, stimulation variables remained constant except during input/output curves.

During the first 60 min of registration, slices were exposed to normal ACSF. After 30 min, 25 consecutive replicates of the amplitude of the population spike produced by the conditioning stimulus were recorded. Pairs of stimulation pulses were then generated with interpulse intervals of 12, 15, 20, 25, and 30 msec. The amplitude of the population spike produced by the second pulse of the pair (test-pulse) was noted. Ten consecutive measurements were made at each interpulse interval. Finally an input/output curve was generated and recorded by the computer.

(+)-Etomidate at concentrations of $2 \times 10^{-6}$, $5 \times 10^{-6}$, or $2 \times 10^{-5}$ M dissolved in ACSF, was perfused between 60 and 120 min. The same measurements as in the control period were then performed again in 90–120 min. Between 120 and 270 min, slices were perfused with normal ACSF. Measurements were repeated at 180 and 240 min to observe a possible reversal of the effects of etomidate.

Table 1. Mean (± SEM) Threshold and Maximal Amplitude of Population Spike at Different Times after Administration of (+)-Etomidate

| | Control | Drug (30 min) | Wash (60 min) | Wash (120 min) |
|---|---|---|---|---|
| $2 \times 10^{-5}$M | | | | |
| Threshold (V) | 4.74(0.1) | 4.74(0.3) | 5.32(0.6) | 4.92(0.5) |
| Amplitude (mV) | 8.41(1.20) | 7.59(1.0) | 8.19(1.1) | 8.86(1.0) |
| $5 \times 10^{-6}$M | | | | |
| Threshold (V) | 4.53(0.22) | 5.05(0.22) | 5.41(0.2) | 5.23(0.2) |
| Amplitude (mV) | 9.01(1.2) | 8.52(1.2) | 8.33(1.5) | 8.3(1.4) |
| $2 \times 10^{-6}$M | | | | |
| Threshold (V) | 4.88(0.28) | 5.05(0.30) | 5.05(0.3) | 5.05(0.3) |
| Amplitude (mV) | 6.37(0.5) | 6.41(0.5) | 6.30(0.4) | 5.95(0.6) |

No significant changes versus control using Wilcoxon matched pairs signed ranks test.

In other experiments (+)-etomidate was replaced by (−)-etomidate $2 \times 10^{-5}$ M ($n = 3$). In a further series of experiments with $2 \times 10^{-5}$ M (+)-etomidate, 134 mM of NaCl was replaced by 134 mM of Na isethionate in the ACSF between 120 and 140 min ($n = 3$).

Mean population spike amplitudes evoked by the test pulse were calculated as percentages of mean conditioning pulse population spike amplitude for each slice and for each group of measurements. Results from individual slices were then pooled.

## Results

Table 1 shows the mean threshold and maximal amplitude of the population spike during input/output curves during control periods, after 30 min exposure to the drug, and after 60 and 120 min washout after drug. The concentrations of (+)-etomidate used did not systematically change EPSP slope or population spike threshold and amplitude. Table 1 also shows that population spike threshold and amplitude remained similar during the experimental period, demonstrating the stability of the slice preparation.

In the control period during stimulation with pairs of pulses, the population spike evoked by the test pulse always had a larger amplitude than the population spike evoked by the conditioning pulse. This is shown in the oscilloscope photograph in Fig. 3(*A*). In normal conditions recurrent inhibition is usually masked by paired-pulse facilitation (22). During the control period paired-pulse facilitation averages from 20 to 50% and increases with interpulse interval. This can be seen in Figure 2, in which the mean (± SEM) amplitude of the orthodromic population spike evoked by the test-pulse is shown as a percentage of the mean amplitude of the population spike evoked by the conditioning pulse at different interpulse intervals.

Addition of (+)-etomidate $2 \times 10^{-6}$ M to the perfusion fluid did not greatly alter pulse-paired induced inhibition or facilitation (Fig. 2(*A*). (+)-etomidate $5 \times 10^{-6}$ M (Fig. 2(*B*)), produced an approximately 50% decrease in the amplitude of the population spike evoked by the test-pulse at all interpulse intervals. This effect was reversed by 2 hr of washout in normal ACSF (Fig. 2(*B*)). (+)-Etomidate $2 \times 10^{-5}$ M almost completely inhibited the population spike evoked by the test-pulse at all interpulse intervals from 12 to 300 msec (Figs. 2(*C*), 3(*B*), 4(*A*), (*B*)). These effects were still present, although diminished, after a 2-hr washout period in normal ACSF (Fig. 2(*C*)).

The concentration of (+)-etomidate producing a 50% reduction in the mean amplitude of the population spike evoked by a test pulse versus the mean amplitude of the population spike evoked by the conditioning pulse ($IC_{50}$) was graphically estimated as $6 \times 10^{-6}$ M at an interpulse interval of 15 msec.

In three slices the same experiment as reported above was repeated with (−)-etomidate $2 \times 10^{-5}$ M in place of (+)-etomidate. (−)-Etomidate was without effect on paired-pulse inhibition at this dose (Fig. 5(*A*), (*B*)).

In three further experiments, 134 mM of NaCl in the ACSF was replaced by 134 mM Na isethionate. The isethionate ion is too large to pass through the $Cl^-$ ion-channel and does not alter ACSF pH. In these three experiments the inhibition of the test pulse population spike amplitude produced by (+)-etomidate $2 \times 10^{-5}$ M was completely reversed by isethionate. Changing back from isethionate ACSF to normal ACSF restored the (+)-etomidate-produced inhibition (Fig. 3(*C*), (*D*), (*E*)).

## Discussion

Early pharmacological studies suggested a GABA-mimetic action for etomidate (23). The same authors demonstrated that uptake of [$^{14}$C]-glutamate and [$^{3}$H]-

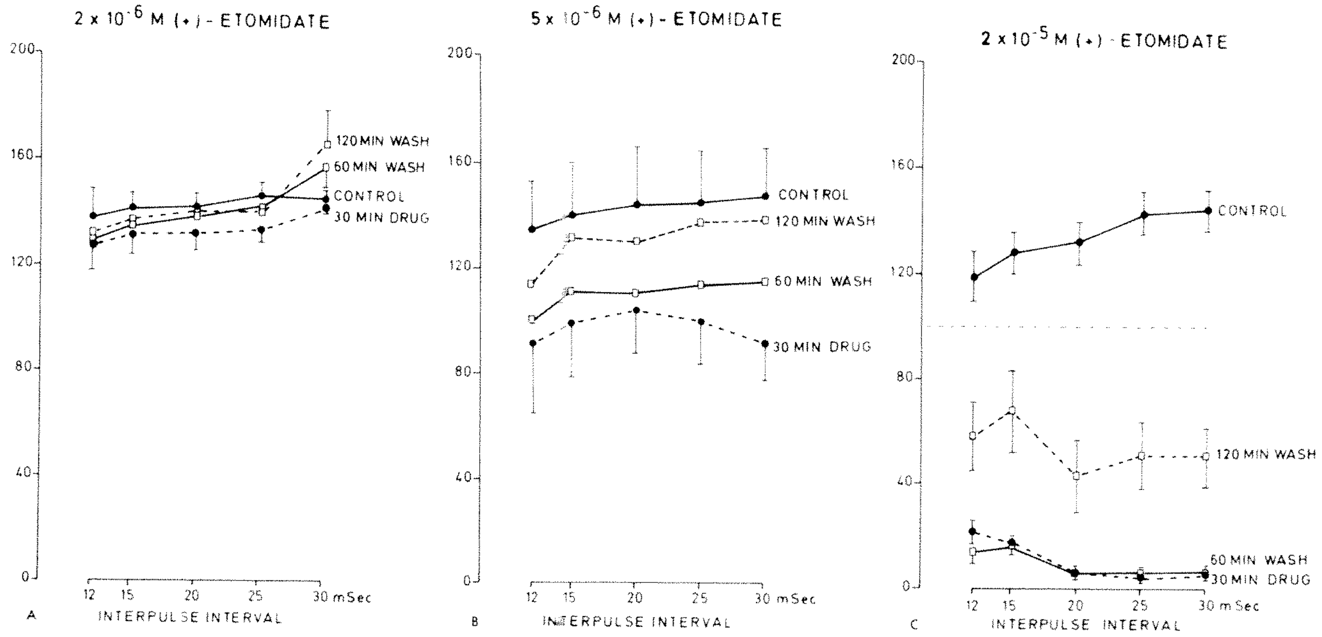


Figure 2. Effects of different concentrations of (+)-etomidate on mean (± SEM) population spike amplitude evoked by test-pulse as a percentage of mean population spike amplitude evoked by conditioning pulse at different interpulse intervals (msec). (*A*) (+)-etomidate 2 × $10^{-6}$ M. (*B*) (+)-etomidate 5 × $10^{-6}$ M. (*C*) (+)-etomidate 2 × $10^{-5}$ M. Symbols: ●—●, control period; -●- - -●-, 30-min exposure to drug; □—□, 60 min wash-out of drug with ACSF, -□- - -□-, 120-min wash-out of drug with ACSF ($n$ = 5 per (+)-etomidate concentration).

GABA into rat brain slices was unaffected by 0.2 mM (+)- or (−)-etomidate. Later biochemical studies demonstrated that (+)-etomidate did not bind to the GABA or benzodiazepine receptors at normal brain concentrations (10). Like barbiturates, (+)-etomidate was shown to increase $^3$H-diazepam binding, suggesting a similar mechanism of action (10). Study and Barker (24) have shown that barbiturates increase the effectivity of GABA-ergic inhibition by increasing the open time of Cl$^-$ ion-channels.

Physiologic and pharmacologic evidence shows that hippocampal pyramidal neuron inhibition is mediated by excitation of GABA-ergic basket cells by collaterals of axons of pyramidal neurones (13,14); by subsequent inhibition of pyramidal neurones by GABA released from basket cells (25); the inhibition being caused by chloride-ion flux through the membrane (16,17,26). The opening of chloride ion channels shunts EPSPs away from the threshold for action potential generation, because the chloride equilibrium potential (approx −80 mV) is greater than the resting membrane potential. Opening chloride ion channels, therefore, inhibits neuronal firing. This system was activated by paired-pulse stimulation, and the effects of etomidate isomers was examined.

(+)-Etomidate caused an increase in paired-pulse inhibition, indicating a drug-induced enhancement of GABA-ergic inhibition. This effect was stereospecific because (−)-etomidate was inactive. (+)-Etomidate had a graphically estimated IC$_{50}$-value for enhanced GABA-ergic inhibition of 6 × $10^{-6}$ M at the 15-msec interpulse interval. This value correlates well with concentrations of (+)-etomidate required in the brain in order to induce hypnosis and produce anticonvulsant activity (27). This value also correlates with the concentration required to stimulate $^3$H-diazepam binding to forebrain membranes by 50% (10 $\mu$M) (10), but is lower than the value of 100 $\mu$M required to stimulate $^3$H-GABA binding (28). The experiments in which isethionate was used to replace Cl$^-$ ions in the ACSF demonstrated that the actions of (+)-etomidate on hippocampal recurrent inhibition were chloride-ion dependent like those of GABA and pentobarbital. Further, the increase in GABA-ergic inhibition produced by (+)-etomidate was shown to occur for interpulse intervals between 12 and 300 msec.

Both barbiturates and benzodiazepines enhance inhibitory GABA-ergic neurotransmission in a chloride-dependent manner (17–19, 26). The finding that etomidate, a drug with a completely different structure, shows this neurophysiologic action strengthens the suggestion that the similar hypnotic and anticonvulsant effects of these three types of drugs result from the same primary mechanism of action. The effect of these drugs on chloride-ion flux is achieved in dif-

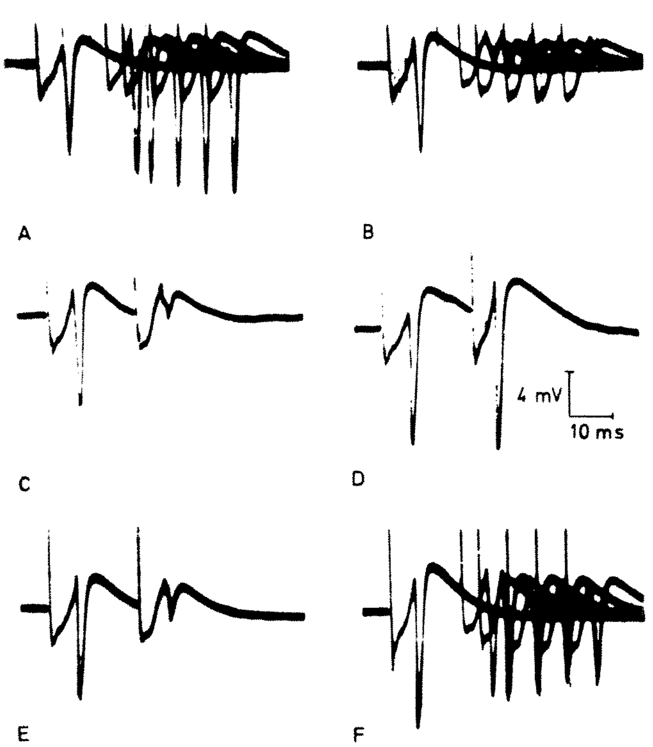


Figure 3. Oscilloscope photographs of field potentials evoked from $CA_1$ pyramidal cells after stimulation of Schaffer collaterals. All photographs from the same slice. (*A*) First upward deflection is the stimulation artefact produced by the conditioning pulse. The conditioning pulse evokes a positive deflection (field EPSP), which is interrupted by a fast negative deflection (population spike). Other field potentials of the same form are evoked by test-pulse stimulations at interpulse intervals of 12, 15, 20, 25, and 30 msec. The traces are superimposed, one above another. Note that the potentials evoked by the test-pulse are larger than the potentials evoked by the conditioning pulse. (*B*) After 30 min exposure to (+)-etomidate $2 \times 10^{-5}$ M the conditioning pulse still evokes a normal field potential. However, the population spikes produced by the test pulses at the same interpulse intervals are almost completely abolished. (*C*) Same time as Fig. 3(*B*) but shows the field potentials evoked by a stimulation pulse pair at a single interpulse interval. Note inhibition of second population spike by (+)-etomidate. Perfusion was then switched to ACSF, where NaCl was replaced by Na isethionate. (*D*) In Na isethionate containing ACSF, the (+)-etomidate-induced inhibition of the population spike evoked by the second stimulation pulse is reversed. Signals are larger because of increased density of ACSF. (*E*) When perfusion with normal ACSF is restarted, the inhibition of the population spike produced by the test pulse returns. (*F*) After 2 hr of washout in normal ACSF, the effects of $2 \times 10^{-5}$ M (+)-etomidate are partially reversed.

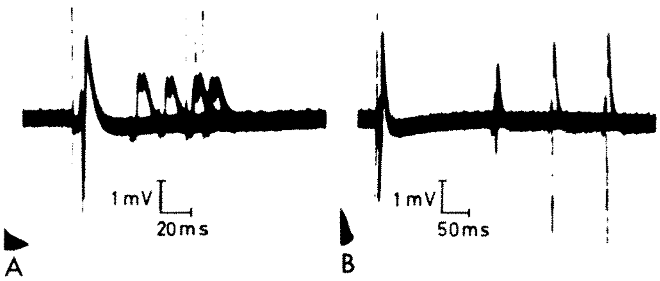


Figure 4. Duration of (+)-etomidate $2 \times 10^{-5}$ M inhibition of population spike evoked by the test pulse. Interpulse intervals from 30 to 300 msec.

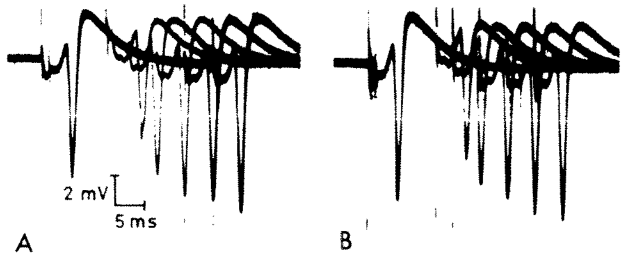


Figure 5. Oscilloscope photograph of field potentials evoked by conditioning pulse and test-pulse at interpulse intervals of 12, 15, 20, 25, and 30 msec. (*A*) Control condition; (*B*) 30 min perfusion with (−)-etomidate $2 \times 10^{-5}$ M. (−)-Etomidate has no effect on paired-pulse inhibition.

ferent ways. Biochemical evidence shows that benzodiazepines and GABA act at distinct sites within the GABA-receptor complex. The actual site where barbiturates and etomidate act is unclear from binding experiments (29), however, the availability of new ligands such as [$^{35}$S]*t*-butylbicyclophosphorothionate (30) may help to clarify this problem soon. Clinical differences between barbiturates, benzodiazepines, and etomidate would, therefore, depend on the specificity of the primary effect on neuronal inhibition, and on individual drug pharmacokinetics.

In conclusion, together with earlier biochemical experiments, the present study demonstrates that in the guinea pig hippocampus etomidate dose-relatedly, stereospecifically, and reversibly increases GABA-ergic pulse-paired inhibition in a chloride-dependent fashion. This increase in pulse-paired inhibition occurs at bath concentrations similar to those concentrations required in the brain for hypnosis and anticonvulsant activity.

## References

1. Janssen PAJ, Niemegeers CJE, Marsboom RPH. Etomidate, a potent non-barbiturate hypnotic: intravenous etomidate in mice, rats, guinea-pigs, rabbits and dogs. Arch Int Pharmacodyn Ther 1975;214:92–132.
2. Desmedt LKC, Niemegeers CJE, Lewi PJ, Janssen PAJ. Antagonism of maximal metrazol seizures and its relevance to an experimental classification of anti-epileptic drugs. Arzneimittelforsch 1976;26:1592–603.
3. Ashton D, Wauquier A. Effects of some anti-epileptic, neuroleptic and gabaminergic drugs or convulsions induced by D,L-allylglycine. Pharmacol Biochem Behav 1979b;11:221–6.
4. Ashton D. Diazepam, pentobarbital and D-etomidate produced increases in bicuculline seizure threshold; selective antagonism by RO15-1788, picrotoxin, and (±)-DMBB. Eur J Pharmacol 1983;94:319–25.

5. Ashton D, Wauquier A. Behavioural analysis of 15 anti-convulsants in the amygdaloid kindled rat. Psychopharmacology 1979a;65:7–13.
6. Wauquier A, Ashton D, Clincke G, Niemegeers CJE, Janssen PAJ. Etomidat, ein barbituratfreies Hypnotikum, anti-konvulsive, anti-anoxische, und hirnprotektive Wirkung in Tierexperiment. In: Opitz A, Degen R, eds. Anästhesie bei zerebralen Krampamfällen und Intensivtherapie des Status Epilepticus. Erlangen, Verlagsgesellschaft, 1980:183–203.
7. Van Der Starre P. Etomidat als schnellwirksame antiepileptische Substanz. In: Opitz A, Degen R, eds. Anästhesie bei zerebralen Krampfamfällen und Intensivtherapie des Status Epilepticus. Erlangen: Verlagsgesellschaft, 1980:205–8.
8. Hoffman P, Schockenhof P. Etomidat als antikonvulsive Substanz. Der Anästhesist 1984;33:142–4.
9. Ashton D, Fransen J, Wauquier A. In vivo interactions between agonists and antagonists of the GABA-benzodiazepine-chloride ionophore receptor complex in a model of hypoxic hypoxia. In: Wauquier A, Borgers M, Amery WK, eds. Protection of tissues against hypoxia. Amsterdam: Elsevier Biomedical Press, 1982:115–9.
10. Ashton D, Geerts R, Waterkeyn C, Leysen JE. Etomidate stereospecifically stimulates forebrain but not cerebellar, $^3$H-diazepam binding. Life Sci 1981;29:2631–6.
11. Thyagaran R, Ramanjaneyulu, Ticků MK. Enchancement of diazepam, and GABA binding by (+) etomidate and pentobarbital. J Neurochem 1983;41:578–85.
12. Kandel ER, Spencer WA, Brinley FJ. Electrophysiology of hippocampal neurons. I. Sequential invasion and synaptic organization. J Neurophysiol 1961;24:225–42.
13. Anderson P, Eccles JC, Løyning Y. Location of postsynaptic inhibitory synapses on hippocampal pyramids. J Neurophysiol 1964a;27:592–607.
14. Anderson P, Eccles JC, Løyning Y. Pathway of postsynaptic inhibition in the hippocampus. J Neurophysiol 1964b;27:608–19.
15. Schwartzkroin PA. Characteristics of CA$_1$, neurons recorded intracellularly in the hippocampal in vitro slice preparation. Brain Res 1975;85:423–36.
16. Alger BE, Nicoll RA. Feed-forward dendritic inhibition in rat hippocampal pyramidal cells studied in vitro. J Physiol 1982a;328:105–23.
17. Alger BE, Nicoll RA. Pharmacological evidence for two kinds of GABA-receptor in rat hippocampal pyramidal cells studied in vitro. J Physiol 1982b;328:125–41.
18. Lee HK, Dunwiddie TV, Hoffer BJ. Interaction of diazepam with synaptic transmission in the in vitro rat hippocampus. Naunyn Schmiedebergs Arch Pharmakol 1979;309:131–6.
19. Wolf P, Haas H. Effects of diazepines and barbiturates on hippocampal recurrent inhibition. Naunyn Schmiedebergs Arch Pharmakol 1977;299:211–8.
20. Langmoen TA, Anderson P. The hippocampal slice in vitro: a description of the technique and some examples of the opportunities it offers. In: Kerkut GA, Wheal HV, eds. Electrophysiology of isolated mammalian C.N.S. preparations. London, Academic Press, 1981:51–107.
21. Anderson P, Blackstad TW, Skrede KK. Unit analysis of hippocampal population spikes. Exp Brain Res 1971;13:208–21.
22. Turner RW, Richardson JL, Miller JJ. Ephaptic interactions contribute to paired-pulse and frequency potentiation of hippocampal field potentials. Exp Brain Res 1984;54:567–70.
23. Evans RN, Hill RG. GABA-mimetic action of etomidate. Experientia 1978;34:1325–6.
24. Study RE, Barker JL. Diazepam and (−) pentobarbital: fluctuation analysis reveals different mechanisms for the potentiation of GABA responses in cultured central neurons. Proc Nat Acad Sci USA, 1981;78:7180–4.
25. Curtis DR, Johnston GAR. Amino-acid transmitters in the central nervous system. Ergeb Physiol 1974;69:97–188.
26. Wong EHF, Leeb-Lundberg LMF, Teichberg VI, Olsen RW. $\gamma$-Aminobutyric acid activation of $^{36}$Cl-flux in rat hippocampal slices and its potentiation by barbiturates. Brain Res 1984;303:267–75.
27. Lewi PJ, Heykants JJP, Janssen PAJ. Intravenous pharmacokinetic profile in rats of etomidate, a short acting hypnotic drug. Arch int Pharmacodyn Ther 1976;220:72–85.
28. Willow M. A comparison of the actions of pentobarbitone and etomidate on [$^3$H] GABA binding to crude synaptosomal rat brain membranes. Brain Res 1981;220:427–31.
29. Olsen RW. Drug interactions at the GABA receptor ionophore complex. Annu Rev Pharmacol Toxicol 1982;22:245–77.
30. Cole LM, Lawrence LJ, Casida JG. Similar properties of [$^{35}$S]*t*-butylbicyclophosphorethionate receptor and coupled components of the GABA-receptor-ionophore complex in brains of human, cow, rat, chicken and fish. Life Sci 1984;35:1755–62.

# Hospitalization for Miscarriage and Delivery Outcome among Swedish Nurses Working in Operating Rooms 1973–1978

H. Anders Ericson, MPolSc, and A. J. Bengt Källén, MD, PhD

ERICSON HA, KÄLLÉN AJB. Hospitalization for miscarriage and delivery outcome among Swedish nurses working in operating rooms 1973–1978. Anesth Analg 1985;64:981–8.

*All infants born in 1973–1978 to nurses working in anesthesiology or as operating room nurses were identified from a nationwide registry of all births in Sweden, a registry of hospitalized spontaneous and legally induced abortions that covers 70% of Sweden, and a nurse registry (n = 1323). For comparison, a group was formed that consisted of nurses working in medical wards (n = 1382). Delivery outcome was also compared with the estimate expected from nationwide figures. No statistically significant differences were seen, but infants of the anesthesiology/operating room nurses had a slightly higher perinatal death rate and a slightly higher rate of preterm births and low birth weights than infants in the comparison group and the nationwide average. On the other hand, the malformation rate was lower in the infants of anesthesiology/operating room nurses than in the control group or nationwide average. A case–control study within the group of anesthesiology/operating room nurses was performed. Questionnaires were sent to 75 nurses (25 cases whose infants died or had serious malformations; 50 controls whose infants were normal); 74 responded. The only difference in working conditions for cases and controls was that the cases had worked after the twenty-eighth week of pregnancy more often than the controls. However, this finding was restricted to nurses whose infants were malformed, and work after the twenty-eighth week cannot affect malformation rate. Work in anesthesiology or operating rooms had no effect on the incidence of hospitalization for miscarriage, perinatal deaths, or malformations detected in the neonatal period.*

Key Words: TOXICITY—teratogenicity, trace concentrations. ANESTHETICS, GASES—trace concentrations.

Since the first report on an apparently high rate of miscarriages among female anesthesiologists (1), many papers have been published on the reproductive hazards of working with volatile anesthetics. These studies have been reviewed (2–4), and the pitfalls and uncertainties of the various studies have been pointed out. The results of most published studies support the hypothesis that a reproductive hazard exists, but some studies have not been able to verify this (3,5). Most studies were questionnaire studies. The problems involved in data collection in questionnaire studies have recently been discussed (6). One important complication is a low response rate. In the large American study (7), the average response rate was 54% but varied in different groups between 76% (an exposed group) to 42% (a control group).

We have previously published a registry study (3) on delivery outcome among Swedish women who, in either 1973 or 1975, had worked in operating rooms during at least half of their pregnancies. No deviations from expected rates of threatened abortion, birth weight distribution, perinatal mortality, or malformation rate were seen; but we observed a possible increased rate of short pregnancies (less than 37 weeks). The study (3) comprised 494 deliveries and is, as far as we know, the only study so far based on data taken from registries where memory bias or other causes of bias in data collection are minimized. The present study extends our previous study and covers the period 1973–1978, but it is restricted to registered nurses.

## Material and Methods

A Medical Birth Registry was initiated in Sweden in 1973. It contains summaries of the standardized records for maternal health care, delivery units, and pediatric examinations of the newborn infants. The registry thus contains medical information on each delivery in Sweden, with less than one percent for which information is lacking. Each woman and infant is identified with his or her personal identification number, a number given shortly after birth to each Swedish

---

Received from the National Board of Health and Welfare, Stockholm and the Department of Embryology, University of Lund, Lund, Sweden. Accepted for publication May 20, 1985.

Address correspondence to Dr. Källén, Department of Embryology, Biskopsgatan 7, S-223 62 Lund, Sweden.

© 1985 by the International Anesthesia Research Society

citizen. The identification number of each individual is kept for life and is used in all types of central registration.

All registered nurses in Sweden are listed in a central registry (the Nurse Registry), also based on the personal identification numbers. This registry is updated in September of each year when the nurses are required to update their current address and working situation.

The Medical Birth Registry has been linked to the Nurse Registry. For each birth to a registered nurse, information was added to the Medical Birth Registry record on working conditions for the year before and the year in which birth took place so that all infants born to registered nurses could be identified with maternal working conditions.

A central registry also exists for all hospitalizations in nonpsychiatric hospitals in Sweden. This is an administrative registry, but the discharge diagnoses are recorded according to the International Classification of Diseases (ICD), eighth revision (8). From these data, all instances of hospitalization because of spontaneous or legal abortion form a Registry of Abortions. Again, each woman is identified by her personal identification number. This registry, however, covers only about 70% of Sweden, as some counties do not participate. In most hospitals, only a small proportion of patients undergoing legal abortions are hospitalized, and the registry therefore does not give the actual number of legal abortions. Nonetheless it can be used for comparing legal abortion rates in two groups of women.

In Sweden a majority of women with spontaneous abortions that require medical care are hospitalized, and therefore information on the abortion enters the registry. The rate of spontaneous abortions registered is about 8–9% of all known pregnancies, with some variation between counties due to varying hospitalization rates. Both medical and social factors may influence hospitalization rates, and small differences in rate of hospitalized spontaneous abortions are therefore difficult to interpret. The Registry of Abortions is linked to the Nurse Registry, and thus the working conditions for a nurse can be determined for the year she has an abortion.

From these two sets of records—the Medical Birth Registry and the Registry of Abortions—two groups of registered nurses were selected and compared. The first group consisted of all nurses who worked as either anesthesiology or operating room nurses during the years before and of a delivery or during the year of an abortion. The second group consisted of all nurses who worked in internal medicine wards on the same schedule as group 1 with regard to childbirth and abortion.

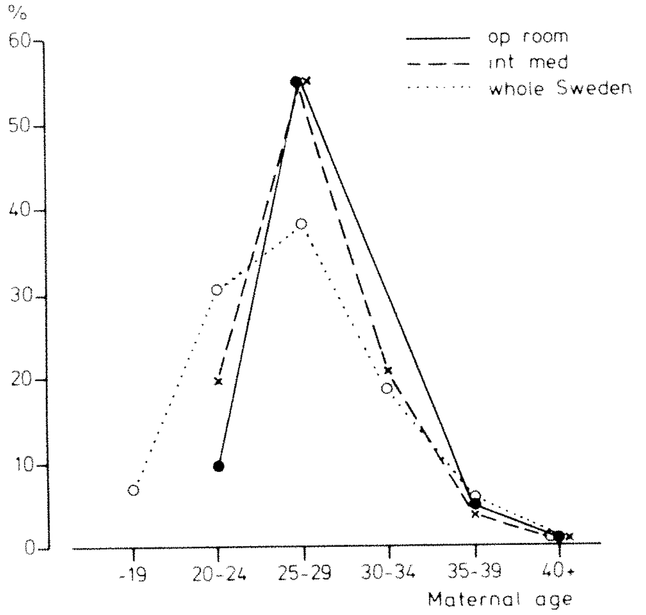


Figure 1. Maternal age distribution in anesthesiology and operating room nurses, in nurses working in medical wards, and in all women in Sweden, 1973–1978.

For each group, the number of hospitalizations for spontaneous abortions, legal abortions, and deliveries was determined. The number of infants born, the number of stillbirths, and the number of liveborns dead within seven days was determined. In the Medical Birth Registry, malformation diagnoses are given as ICD codes. This variable concept is standardized to some extent by restriction to so-called significant malformations and exclusion of some very variable ones, e.g., undescended testicles, subluxation of the hips, hydroceles, postaxial polydactyly, nevus. In order to obtain more detailed information on the presence of malformations, the Registry of Congenital Malformations (9) was used. This registry gives a more detailed description of malformations present. Furthermore, some malformed infants are reported only in that registry, others only in the Medical Birth Registry (10). By using both registries, a more complete ascertainment of malformation diagnoses was obtained. For each infant identified in the Medical Birth Registry (alive or not, malformed or not), the birth weight (related to pregnancy length) and (for liveborns) the Apgar score at 5 min are recorded. Apgar score distributions, the incidences of perinatal death and significant malformations, gestational length, and birth weight were compared between the two groups and with all women in Sweden who delivered during these years, standardizing for year of birth, delivery unit, maternal age, and parity.

The study was followed up with a case–control within-group study. Women working in anesthesiology or in operating rooms whose infants died perinatally or had a severe congenital malformation were selected as "cases." For each case, two controls (pregnancies resulting in normal childbirth) were chosen from among the same group of nurses (group 1, above). A simple questionnaire was sent to each woman, asking for details on her occupation during her pregnancy.

## Results

Figure 1 shows maternal age and parity distribution among two groups of nurses and all women in Sweden. Both groups of nurses had a maternal age distribution that deviated from that of all women in Sweden, i.e., no deliveries before the age of 20 and a shift to the 25–29 yr age group. There is a slight difference between the two groups, with a slightly higher age for nurses working in anesthesiology or as operating room nurses than for nurses working in medical wards. This fact can be explained by the longer training period required for nurses in the former group. Parity graphs (Fig. 2) show that nurses who delivered during this period are more often of parity 1 or 2 than the average woman in Sweden. Again a slight difference exists between the two groups of nurses.

Table 1 presents, for the two groups of nurses, the number of births each year, the number of stillbirths, the number of infants who died within the first week, and the number of infants with a significant malformation. The low number of births in 1978 is due to the fact that, at the time of data collection, this year was not completely documented in the Medical Birth Registry. The expected number of dead or malformed infants is given (in parentheses), calculated from the complete Medical Birth Registry with standardization for year of birth, delivery hospital, maternal age, and parity. These figures thus give the projected numbers for samples of these sizes drawn randomly from all births in Sweden, but with the same distribution of year of birth, delivery hospital, maternal age, and parity as our studied sample. It can be seen that the total perinatal mortality among infants born to nurses working in anesthesiology or in operating rooms is very close to the expected value in a random sample, but that the perinatal mortality of infants born to nurses working in medical wards is somewhat, but not significantly, lower than the expected rate (11 found, 16.5 expected, $\chi^2 = 1.8$, 1 *df*). On the other hand, the rate of infants with any malformation is lower than expected in the group of anesthesiology and operating room nurses but higher in the group who worked in the medical ward. The difference reaches statistical significance ($\chi^2 = 4.3$, $P < 0.05$, 1 *df*) for the former group, but not for the latter ($\chi^2 = 1.5$, 1 *df*).

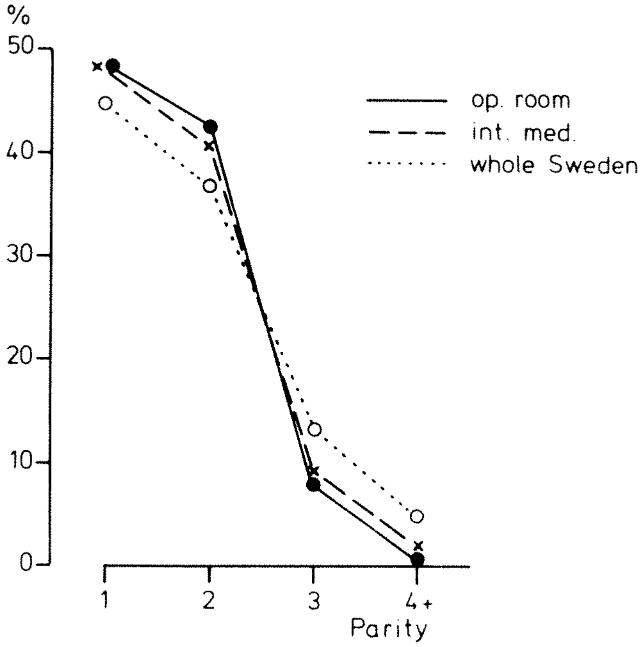


Figure 2. Parity distribution in anesthesiology and operating room nurses, in nurses working in medical wards, and in all women in Sweden, 1973–1978.

Table 2 shows that the sex ratio is the same among infants of the two groups of nurses and is the same as that found in the general population. The number of twin births is greater in infants born to nurses working in operating rooms than in those born to women working in medical wards. Among the anesthesiology and operating room nurses, the number of twin births is also higher than that expected for the country as a whole ($\chi^2 = 2.6$, 1 *df*), while in the group of medical ward nurses, the registered number is slightly lower than that expected nationwide. This phenomenon occurred despite the fact that the age compositions of the two groups of women are relatively similar (Fig. 1). The difference between the groups does not reach statistical significance ($\chi^2 = 3.1$, 1 *df*).

The distribution of pregnancy duration in the two groups of nurses is similar and agrees with that expected nationwide. A total of 4.4% of infants born to nurses working in anesthesiology or in operating rooms weighed less than 2500 g, which is slightly (but not statistically significantly) more than that expected from the whole country. The corresponding rate for infants born to nurses working in medical wards is 3.3%. As

Table 1. Characteristics of Infants Born to Two Groups of Nurses in Sweden, 1973–1978

| Year | Number of infants | Stillbirths | Livebirths dead < 7 days | Significant malformation | Any malformation |
|---|---|---|---|---|---|
| Group #1: Nurses working in anesthesiology or as operation room nurses | | | | | |
| 1973 | 221 | 2 | 2 | 2 | 9 |
| 1974 | 273 | 0 | 0 | 1 | 7 |
| 1975 | 249 | 2 | 3 | 6 | 14 |
| 1976 | 245 | 2 | 1 | 4 | 8 |
| 1977 | 247 | 0 | 2 | 4 | 8 |
| 1978 | 88 | 1 | 1 | 0 | 4 |
| Total | 1323 | 7 (8) | 9 (7.2) | 17 (21) | 50 (67) |
| Group #2: Nurses working in wards for internal medicine | | | | | |
| 1973 | 274 | 4 | 2 | 7 | 15 |
| 1974 | 257 | 1 | 1 | 6 | 14 |
| 1975 | 242 | 0 | 0 | 3 | 12 |
| 1976 | 269 | 0 | 1 | 9 | 23 |
| 1977 | 272 | 2 | 0 | 2 | 10 |
| 1978 | 68 | 0 | 0 | 0 | 2 |
| Total | 1382 | 7 (8.5) | 4 (8) | 17 (22) | 76 (66) |

Expected numbers are given in parentheses. These are calculated from data for the whole country after standardization for year of birth, maternity clinic distribution, maternal age, and parity.

both gestational length and birth weight are influenced by social factors, the best comparison is probably between the two groups of nurses; the rate of low-birth-weight infants is thus higher in group 1 (anesthesiology/operating room) than in group 2 (medical ward), but this difference is not statistically significant ($\chi^2 = 2.05$, 1 *df*). Similarly, there is a statistically insignificant increased rate of infants with an Apgar score less than seven at 5 min in group 1 compared to group 2.

In Table 1, malformation rates were compared using a relatively crude concept: "significant" malformation. Table 3 lists the diagnoses identified. In Table 3, not only diagnoses given in the Medical Birth Registry are listed but also diagnoses identified from the Registry of Congenital Malformations. A total of 53 infants were found with diagnosed malformations among the infants born to nurses in group 1 (4.0%); the corresponding figure for the infants born to women in group 2 is 79 (5.7%). The difference is statistically significant ($\chi^2 = 4.1$, 1 *df*, $P < 0.05$). The expected rate from the total population is about 5%, which is close to the rate of the total group of infants born to both groups of nurses (4.9%).

As the number of infants in the two groups is roughly comparable, the absolute numbers of each type of malformation can be directly compared. Only for two diagnoses are there marked differences: any congenital heart defect (7 in group 1; 12 in group 2—in group 2 patent ductus arteriosus was diagnosed in four neonates), and a positive Ortolani phenomenon (7 and 22, respectively). No specific malformation is more common in group 1 than in group 2.

As stressed in the Material and Methods section, absolute rates of spontaneous or legal abortions are difficult to estimate from the available data, but rates of the two groups of nurses can be compared. In the group that worked in operating rooms, a total of 1323 births, 87 spontaneous abortions, and 26 legal abortions were identified. In the group that worked in medical wards, 1382 births, 85 spontaneous abortions, and 28 legal abortions were identified. Thus, the rate of all identified pregnancies ending in spontaneous abortion was 6.1% in group 1 and 5.7% in group 2. The low rates are explained to at least some extent by the fact that the Registry of Abortions covers only 70% of the country. Because of the similar rates in the two groups, 84 spontaneous abortions were expected in the first group (in which 87 were found), a difference that is not significant.

In the case–control study, all 25 infants who died perinatally or had a severe malformation were selected from the group of infants born to nurses in group 1. For each, two controls born the same year as the case were chosen from the same group of infants, from the same 5-yr maternal age stratum, and from the same parity (1,2,3+) stratum as the case. To each one of these 75 nurses, a questionnaire was sent; 74 replied (letters to the 75th were returned unopened with the note that the addressee was unknown in

Table 2. Some Characteristics of the Infants Born to Nurses Working in Anesthesiology/Operating Rooms or in Medical Wards

| Characteristic | Mothers worked in anesthesiology/ operating rooms | Mothers worked in medical wards | All Swedish births |
|---|---|---|---|
| Sex ratio | | | |
| Males | 680 | 710 | — |
| Females | 642 | 672 | — |
| Ratio | 1.06 | 1.06 | 1.06 |
| Twin births | | | |
| Observed | 16 (1.22%) | 8 (0.58%) | (0.82%) |
| Expected | 10.7 | 11.30 | |
| Pregnancy length | | | |
| Less than 33 weeks | 16 (1.2%) | 17 (1.2%) | (1.6%) |
| Less than 37 weeks | 97 (7.3%) | 109 (7.9%) | (9.8%) |
| Birth weight | | | |
| Less than 1000 g | 4 (0.3%) | 0 | (0.2%) |
| Less than 1500 g | 9 (0.7%) | 5 (0.4%) | (0.7%) |
| Less than 2500 g | 58 (4.4%) | 46 (3.3%) | (4.5%) |
| Apgar score less than 7 at 5 min | 18 (1.4%) | 10 (0.7%) | (1.5%) |

spite of the fact that all address registers gave that address as the current one). The reply rate is thus nearly 99%.

Table 4 summarizes the responses. There were slightly more nurses working as anesthesiology nurses than as operating room nurses in the case group than in the control group. This ratio is mirrored in a higher general work rate in anesthetic departments, but the difference is not statistically significant. Two nurses had worked in outpatient departments where general anesthesia was probably not common; both were controls. The place of work was not specified for four nurses. Two nurses pointed out that they had hardly been exposed to anesthetic gases (one case; one control). Four worked only half-time (two cases; two controls), and one (a control) had not worked during her first trimester of pregnancy.

The only remarkable difference was in the length of work during pregnancy in the two groups. A total of 14 nurses had stopped work before week 28 (2 cases and 12 controls) ($P < 0.05$): in six of them the neonate had severe malformations that originated long before the 28th week (0 cases and 6 controls); in eight, the infant was dead perinatally (2 cases and 6 controls). The effect of stopping work before week 28, therefore, seems to be more associated with malformations than with perinatal death, which seems biologically improbable.

## Discussion

Data collected in this study gives little evidence for a high incidence of abnormal outcome of pregnancy in registered nurses who worked in anesthesiology and in operating rooms (group 1) during pregnancy. Perinatal death rates were similar to those expected from nationwide data but slightly (although not statistically significantly) higher than in the comparison group: nurses working in medical wards (group 2). The number of registered spontaneous abortions was also somewhat higher in group 1 than in group 2, but the difference was far from statistically significant. On the other hand, the number of malformed infants born to women in the group supposedly exposed to anesthetics was smaller than the number expected from the country as a whole. The difference between the two groups reached statistical significance. It is hard to believe that this occupation can protect against birth defects, but theoretically such an effect could be obtained by increasing the abortion rate of malformed embryos. It is more likely that the finding is random in spite of the statistical significance; many comparisons have been made. Actually, the difference seems to depend to a large extent on a high number of congenital hip subluxations in the group of comparison (group 2, nurses working in medical wards), and this diagnosis is very sensitive to local diagnostic practice for instance. The upper 95% confidence limit for the malformation rate in the exposed group is 5.2%, which is very close to the average risk in the country. No specific type of malformation was seen more frequently in infants born of nurses working in operating rooms than in infants born of nurses working in medical wards.

This conclusion—the apparent lack of reproductive hazards resulting from work in anesthesiology or in

Table 3. Malformations Diagnosed in Infants Born to Nurses Working in Operating Rooms or in Medical Wards

| Diagnosis[a] | Mothers worked in anesthesiology/ operating rooms | Mothers worked in medical wards |
|---|---|---|
| Neural tube defects | 3 | 4 |
| Preauricular tags | 5 | 3 |
| Ear dysplasia | 0 | 1 |
| Cleft lip and/or palate | 3 | 3 |
| Unspecified larynx malformation | 1 | 0 |
| Megacolon | 1 | 0 |
| Anal atresia and cardiac defect | 0 | 1 |
| Patent ductus arteriosus | 0 | 4 |
| Ventricular septal defect | 1 | 0 |
| Cardiac defect and pes calcaneovalgus | 1 | 0 |
| Severe cardiac defect | 1 | 0 |
| Unspecified cardiac defect | 4 | 7 |
| All cardiac defects | 7 | 12 |
| 2 umbilical vessels | 2 | 0 |
| Pes equinovarus | 2 | 4 |
| Metatarsus varus | 0 | 1 |
| Pes calcaneovalgus | 0 | 3 |
| Positive Ortolani phenomenon | 7 | 22 |
| Arachnodactyly | 1 | 0 |
| Positive Ortolani and pes calcaneovalgus | 1 | 0 |
| Thumb duplication | 1 | 0 |
| Unspecified limb reduction | 0 | 2 |
| Foot syndactyly | 0 | 2 |
| Osteogenesis imperfecta | 1 | 0 |
| Chondrodystrophy and microtia | 1 | 0 |
| Unspecified face/skull malformation | 1 | 0 |
| Nevus | 2 | 4 |
| Epidermolysis bullosa | 0 | 1 |
| Retentio testis | 5 | 4 |
| Hydrocele testis | 6 | 6 |
| Hypospadias | 0 | 3 |
| Epispadias | 0 | 1 |
| Urethral atresia/stenosis | 1 | 0 |
| Bilateral renal agenesis | 0 | 3 |
| Down's syndrome | 2 | 1 |
| Total | 53 | 79 |

[a] Malformation diagnoses ascertained from both the Medical Birth Registry and the Registry of Congenital Malformations.

Table 4. Summary of Responses for the Case–Control Questionnaire Study Made Among Operating Room Nurses

| | Cases | Controls |
|---|---|---|
| Type of work | | |
| Anesthesiology | 15 (60%) | 26 (53%) |
| Operating room nurse | 9 (36%) | 22 (46%) |
| Other | 1 | |
| Type of hospital clinic | | |
| Anesthesiology | 13 (52%) | 19 (39%) |
| Central operating unit | 4 (16%) | 5 (10%) |
| Surgical clinic | 1 (4%) | 5 (10%) |
| Obstetrics/gynecology | 1 | 5 |
| ENT | 1 | 4 |
| Ophthalmology | 1 | 0 |
| Plastic surgery | 1 | 0 |
| Thoracic surgery | | 2 |
| Neurosurgery | | 4 |
| Pediatric surgery | | 2 |
| Outpatient department | | 2 |
| Non-specified | 1 | 3 |
| Other information | | |
| Little exposure to anesthetic gases | 1 | 1 |
| Worked half-time | 2 | 2 |
| Stopped work < 28 weeks | 2 | 12 |
| No work first trimester | 0 | 1 |

No. of cases (perinatally dead or severely malformed infants), 25.
No. of controls matched for year of birth, maternal age and parity, 50.
No. of non-responders, 1 (control).

operating rooms—is at variance with most but not all previous studies. There are some possible explanations for this discrepancy.

This study is based on registry data and may be too crude, either with respect to outcome or with respect to exposure. Registration of perinatal deaths is close to 100% correct and unbiased. Registration of malformations is never absolutely complete, but by using both available registries (the Medical Birth Registry and the Registry of Congenital Malformations) it is believed that more than 90% coverage is obtained, at least for surviving infants and for serious malformations. Furthermore, although the fact that a woman works in medical areas may influence the registration of minor malformations (11), it is not likely that the actual type of work done by a nurse will influence that registration to any large extent. The same is true for spontaneous abortions as defined in this study; although probably incomplete, it is not likely that the type of work done by the nurse will influence to any marked extent the probability that she will be hospitalized for a spontaneous abortion and, therefore, be entered into our study.

On the other hand, it should be remembered that the outcomes studied here cover only part of the reproductive failures. Obviously, infertility, sometimes claimed to be the result of exposure to anesthetic gases, cannot be evaluated. This is also true to some extent for early spontaneous abortions, which may not come to medical attention or for which the woman may not be hospitalized. It can be estimated that the spontaneous abortions registered in the Registry of Abortions represent a miscarriage rate of approximately 8–9% of all pregnancies. This means that perhaps 20% of all clinically recognized spontaneous abortions do not require the woman to be hospitalized, are not entered in the registry, or both. To a large extent these are probably relatively early abortions, and it is possible that the occupational hazards in operating rooms are selectively directed to such early miscarriages. Biologically, early miscarriages often have different causes than do late miscarriages; a large proportion of the former are due to gross chromosomal aberrations. The negative outcome of the study with regard to miscarriages can thus be due to the absence of registration of early miscarriages.

Similarly, only birth defects recognizable at birth or during the first weeks of life were studied. It is possible (but there is no evidence) that later developments like mental retardation occur at an increased rate in infants born to women who worked in operating rooms during their pregnancy than in infants born to other nurses.

The information about anesthetic exposure in the registry is crude, indicating only that the nurse worked in anesthesiology or as an operating room nurse. This is the type of exposure data that has been available in most studies on the subject. In the present study, however, the information comes from a registry. The questionnaire follow-up study verified that among 74 nurses asked for information, 73 reported that they actually worked as anesthesiology or operating room nurses during the relevant pregnancy, but two nurses said that exposure to anesthetic gases had been very low (one case, one control).

In the primary analysis, anesthesiology and operating room nurses were treated as one group. It is likely that anesthetic gas exposure is higher for anesthesiology nurses than for operating room nurses, but in previous studies both types have often been regarded as "exposed." The case–control within-group study performed indicated a slight but not statistically significantly increased risk for anesthesiology nurses compared to operating room nurses. This may indicate that group 1 actually has a somewhat higher risk but its presence cannot be demonstrated with certainty, even in a study of this size.

Another explanation for the negative outcome of the study could be that the working environment in operating rooms in Sweden during this time period was so clean that no real exposures occurred among the personnel. A study of this problem (12) showed that this was not the case—only 2 out of 21 operating rooms studied fulfilled the stipulated air exchange requirements (at least 17 complete air changes per hour, at least 2000 $m^3$/hr). Furthermore, time-weighted average halothane concentrations of more than 7 ppm were measured for anesthesiology nurses and of about 2.5 ppm for operating room nurses.

Obviously, the ideal exposure information should include type of anesthetic gases used, air concentrations, and number of hours of exposure. This information cannot be ascertained in the type of study made; and, generally speaking, detailed exposure data are difficult to get for large enough numbers of women to make studies on pregnancy outcome meaningful.

The nature of many earlier studies makes their conclusion on reproductive hazard for anesthesiology and operating room personnel questionable (reviews in 2–4). One main drawback with most earlier studies that gave positive associations between exposure and reproductive hazards is that they were questionnaire studies, often with a high percentage of nonresponders (7) or they were small, with a moderate percentage of nonresponders (13,14). In one postal questionnaire study (6), an increased rate of spontaneous abortions was found in women working in operating rooms where exposure to anesthetic gases was likely. In spite of a relatively low percentage of nonresponders, this group was shown to be markedly atypical with few reported miscarriages among nonexposed women. When identified but unreported pregnancies were included in the analysis, no significant difference in miscarriage rate remained (6). That study underlies the problems in postal questionnaire studies with even moderate nonresponder rates. Also, the actual information given by the responders has been shown to be biased by the hazards thought to exist (15). It can be pointed out that the high malformation rate sometimes observed (14) is mainly due to minor anomalies like skin marks, which are especially sensitive to reporting bias. It is possible that the conclusions drawn from questionnaire studies with sometimes rather high nonresponder rates are false due to shortcomings in the material analyzed, and that the registry data used in the present study are more likely to give correct estimates of the risks involved.

This study has not shown that it is harmless to work in the operating room during pregnancy. What has been shown is that the point estimate of the relative risk to have an infant with a congenital malformation is below 1, and its confidence interval excludes the possibility of any marked effect on the group of malformations that are recognized in the newborn period. It is still possible that specific exposure conditions and the use of specific anesthetic gases may carry a risk, and this should be contemplated in planning work protection. On the other hand, the presence of a congenital malformation in an infant born to an anesthesiology or operating room nurse or the occurrence of a miscarriage should not necessarily be blamed on occupation; it may be due to other explanations, including genetic factors.

## References

1. Vaisman AI. Work in surgical theatres and its influence on the health of anaesthesiologists. Eksp Khir Anest 1967;12:44–9.
2. Ferstandig LL. Trace concentrations of anesthetic gases: a critical review of their disease potential. Anesth Analg 1978;57: 328–45.
3. Ericson A, Källén B. Survey of infants born in 1973 or 1975 to Swedish women working in operating rooms during their pregnancy. Anesth Analg 1979;58:302–5.
4. Axelsson G. Miscarriage after occupational exposure. Aspects of risk assessment in retrospective studies. Thesis, Gothenburg, ISBN-91-7222-630-7, 1983.
5. Rosenberg P, Vänttinen H. Occupational hazards to reproduction and health in anaesthetists and paediatricians. Acta Anaesthesiol Scand 1978;22:202–7.
6. Axelsson G, Rylander R. Exposure to anaesthetic gases and spontaneous abortions: response bias in a postal questionnaire study. Int J Epidemiol 1982;11:250–6.
7. Occupational disease among operating room personnel: a national study. Report of an ad hoc committee on the effect of trace anesthetics on the health of operating room personnel. Anesthesiology 1974;41:321–40.
8. World Health Organization. Manual of the international statistical classification of diseases, injuries, and causes of death. Klassifikation av sjukdomar 1968. Socialstyrelsen, 3rd ed. Stockholm 1973. Geneva: World Health Organization, 1967.
9. Källén B, Winberg J. A Swedish register of congenital malformations. Experiences with continuous registration during 2 years with special reference to multiple malformations. Pediatrics 1968;41:765–76.
10. Ericson A, Källén B, Winberg J. Surveillance of malformations at birth: a comparison of two record systems run in parallel. Int J Epidemiol 1977;6:35–41.
11. Balzar B, Ericson A, Källén B. Delivery outcome in women employed in medical occupations in Sweden. J Occup Med 1979;21:543–8.
12. Göthe CJ. Narcotic gases as industrial hazard (Swedish). Läkartidningen 1976;73:2553–63.
13. Tomlin PJ. Health problems of anaesthetists and their families in the West Midlands. Br Med J 1979:779–84.
14. Corbett TH, Cornell RG, Endres JL, Lieding K. Birth defects among children of nurse-anesthetists. Anesthesiology 1974;41:341–4.
15. Axelsson G, Rylander R. Validation of questionnaire reported miscarriages, malformations and birth weight. Int J Epidemiol 1984;13:94–8.

## Note Added in Proof

Since this paper went to press, Hemminki et al. have published a report in which they observe that exposure to anesthetic gases produced no statistically significant effect on spontaneous abortion rates or on malformation rates. This study is also based on registry material and followed up with questionnaires: Hemminki K, Kyyrönen P, Lindbohm M-L. Spontaneous abortions and malformations in the offspring of nurses exposed to anesthetic gases, cytostatic drugs, and other potential hazards in hospitals, based on registered information of outcome. J Epidemiol Community Health 1985;39:141–7.

ANESTH ANALG
1985;64:989–95

# Control and Accountability of Controlled Substance Administration in the Operating Room

Ronald J. Moleski, Pharm D, Shirlene Easley, BS, RPh, Paul G. Barash, MD, Gil Primer, MS, Nicte-ha Q. Shier, MD, and Robert I. Schrier, MD

MOLESKI RJ, EASLEY S, BARASH PG, PRIMER G, SHIER NQ, SCHRIER RI. Control and accountability of controlled substance administration in the operating room. Anesth Analg 1985;64:989–95.

*Personnel working in the operating room complex may be at increased risk for chemical impairment. It has been proposed that this predisposition may be related to the frequency of use of controlled substances and the inadequate control over distribution of these medications, which frequently exists in the operating room. A system utilizing a pharmacy satellite in the operating room has increased the control and accountability of drug administration practices. Several other alternative systems are also reviewed. Emphasis is placed on the establishment of a quality assurance program to monitor compliance routinely.*

Key Words: ANALGESICS—control systems. ANESTHETICS, INTRAVENOUS—control systems.

Historically, control and accountability of drug administration in the operating room (OR) complex have been difficult, particularly in regard to controlled substances. In general, the use of narcotic agents for "balanced anesthesia" has become quite common. More specifically, the popularity of fentanyl, a highly potent, short-acting narcotic, has also increased considerably, especially as an anesthetic for patients undergoing cardiac operations. The distribution and appropriate safeguards of this large volume of controlled drugs have presented problems for operating room personnel.

Traditionally, the systems for distribution of controlled substances in operating rooms have not provided the accountability and control mandated by Federal and state regulations. This may be related to the urgent and critical nature of surgical and anesthetic practice and the common perception that all drugs must be readily available at a moments' notice. Perhaps the routine daily administration of controlled substances by anesthesiologists minimizes the appreciation for the importance of governmental regulations controlling their use. Increasing attention has been paid to the problem of substance abuse among physicians (1–5). A recent survey indicated that 74% of anesthesia training programs surveyed reported at least one instance of suspected drug dependence among anesthesia personnel (6). The omnipresent availability of drugs has been cited as a potentially significant cause for the relatively high incidence of chemical dependence among anesthesiologists (6).

## The Traditional Distribution System

The controlled substance distribution system commonly employed by most hospitals involves delivery of a floorstock supply of drugs by the pharmacy to the OR nursing station. The quantity of drugs delivered is recorded, and each drug supply is accompanied by a proof-of-use sheet. The drug supply is controlled by the nursing staff, who dispense varying quantities at the request of the anesthesiologist, nurse anesthetist, or surgeon prior to each procedure. Circulating nurses are also responsible for obtaining additional doses during surgical procedures.

Under this system, nurses are required to complete entries on proof-of-use sheets, although they are not actually administering the drugs. This practice circumvents the primary intent of the proof-of-use process. The person actually administering the drug should make the entry on the proof-of-use record, but under this system there may be no accountability for the actual use of a drug after it leaves the nursing station.

---

Received from Yale New Haven Hospital, Yale University School of Medicine, New Haven, Connecticut. Accepted for publication June 6, 1985.

Address correspondence to Dr. Barash, Department of Anesthesiology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510.

© 1985 by the International Anesthesia Research Society

A number of problems are inherent with such a system:

1. Proof-of-use documents often do not match actual stock levels of the drug.
2. There is no record of waste or disposal of controlled substances.
3. There is no quality assurance audit trail that compares drug requisition records against actual drug administration.
4. Controlled substances can be found in nonsecure locations such as anesthesia carts and equipment boxes.
5. Controlled substances are left unattended in operating rooms after surgical procedures have been completed.

This system also results in noncompliance with Federal, state, or Joint Commission for the Accreditation of Hospitals (JCAH) regulations for record keeping.

Federal laws require that the following be recorded:

1. Name, strength, and quantity or volume of controlled substances dispensed or administered.
2. Name of prescriber and individual administering the controlled substance.
3. Date of administration.
4. Name of the patient to whom the controlled substances are administered.
5. Number of units or volume disposed of by the prescriber.
6. Maintenance of controlled substance records for two years.

State laws (in Connecticut)[1] require that

1. Separate records be maintained for the administration of schedule II, III, and IV controlled substances.
2. Records of use of controlled substances be maintained for three years.

The JCAH requires that dosage and time of administration of all anesthetic agents or other drugs administered during the induction of, maintenance of, and emergence from anesthesia must be documented.

Before 1982, the drug distribution system in the OR at Yale–New Haven Hospital was similar to the traditional system. In 1982, the Departments of Anesthesiology, Pharmacy, Nursing, and Security met to assess the existing weaknesses and to devise ways to improve the controlled substance distribution system. As the first step, a set of goals and objectives was developed (Table 1). This led to consideration of a number of alternatives.

Table 1. Goals

1) Clinical care in the OR must not be impeded.
2) Increased accountability of controlled substances dispensed in the OR.
3) Reduction of controlled substance loss and waste.
4) Decreased nursing involvement in dispensing of controlled substances.
5) Placing the burden of accountability on those responsible for the administration of controlled substances.
6) Development of a quality assurance audit trail to compare controlled substance dispensing against the actual drug administration record.
7) Compliance with Federal, state and JCAH regulations.

### *Continuation of the Traditional Dispensing System*

The traditional dispensing system was discarded because of the many problems described earlier (i.e., poor record keeping, lack of control of drug use, lack of an audit trail of drug use).

### *A Machine to Dispense Medications*

Such a system (J. Laycock, personal communication) maintains a record of all drugs dispensed and is activated by three "keys": the patient's addressograph plate, a medication plate, and an operator ID key (issued to each anesthesiologist and nurse anesthetist). It was determined that this system was inadequate for a number of reasons, including initial purchase price, the limited capacity for dispensing large ampules, the necessity of providing a mechanism to bypass the system in the event of mechanical breakdown or lost ID keys, and the difficulty in returning unused medication without leaving gaps in the audit trail. Also, this system would still require an additional full-time pharmacist or technician to maintain drug stock and process records.

### *Individualized Anesthesia Boxes*

Each anesthesiologist would be responsible for his or her own locked drawer. The boxes could then be locked into either an anesthesia cart when in use or into a master security cart when not in use. This system would offer the advantage of individualizing drug supplies and would make anesthesiologists and nurse anesthetists ultimately accountable for their own drug supplies. This system was considered unacceptable because it would require a larger and expensive working inventory of drugs. In addition, anesthesia per-

---

[1] Each state has separate laws governing controlled substance use. The reader should check with state or local authorities for specific regulations.

Table 2. Budget

| | Initial costs | Yearly costs |
|---|---|---|
| 1.0 Full-time employee pharmacy technician | | $15,500 |
| Printing: requisitions, etc. | 350 | 350 |
| Narcotic cabinets (4) | 600 | |
| Miscellaneous supplies | 100 | 100 |
| Total | $1050 | $15,950 |

sonnel did not wish to be personally responsible for large quantities of controlled substances.

### *An Operating Room Pharmacy Satellite*

We ultimately decided to institute an OR pharmacy satellite in the patient "holding area" of the OR complex. Reports of other OR satellites have appeared in the literature and have addressed the issue of accountability in varying degrees (7–9). The satellite is staffed by a pharmacy technician who is supervised by a pharmacist from the central inpatient pharmacy. This system was employed because it directed responsibility for drug distribution to a single individual and provided greater flexibility than a dispensing machine.

The costs for material necessary for establishment of the OR pharmacy satellite were minimal and involved allocation of a small room off the main holding area, installation of double-locked narcotic cabinets for storage of drug supplies, and an additional double-locked cabinet in the holding area for return of unused medications (see below). Additional expenses involved printing requisition forms and other record-keeping documents (Table 2).

The only significant expense of an OR pharmacy satellite is the annual salary of the pharmacy technician (Table 2). However, while utilization of the technician does incur a recurrent annual expenditure, there are other benefits provided by this position. The technician serves as a direct liason with the central pharmacy and can expedite procurement of drug supplies not normally stocked in the OR. The technician also organizes and controls other nonnarcotic drugs stocked in the OR, does all the ordering of drug supplies, and routinely checks drug supplies contained in emergency (code) carts for outdated medications. The system also significantly reduces the personnel time and costs associated with follow-up and investigation of controlled substance discrepancies.

The satellite is staffed on weekdays from 7:00 AM to 3:30 PM. The procedures employed involve two different systems, one for weekdays, and one for after hours and weekends. During fiscal year 1982–1983, approximately 14,000 anesthetic procedures were performed, and a total of 17,000 controlled substance requisitions were processed in the satellite pharmacy. The 17,000 figure includes requisitions for elective as well as emergency cases.

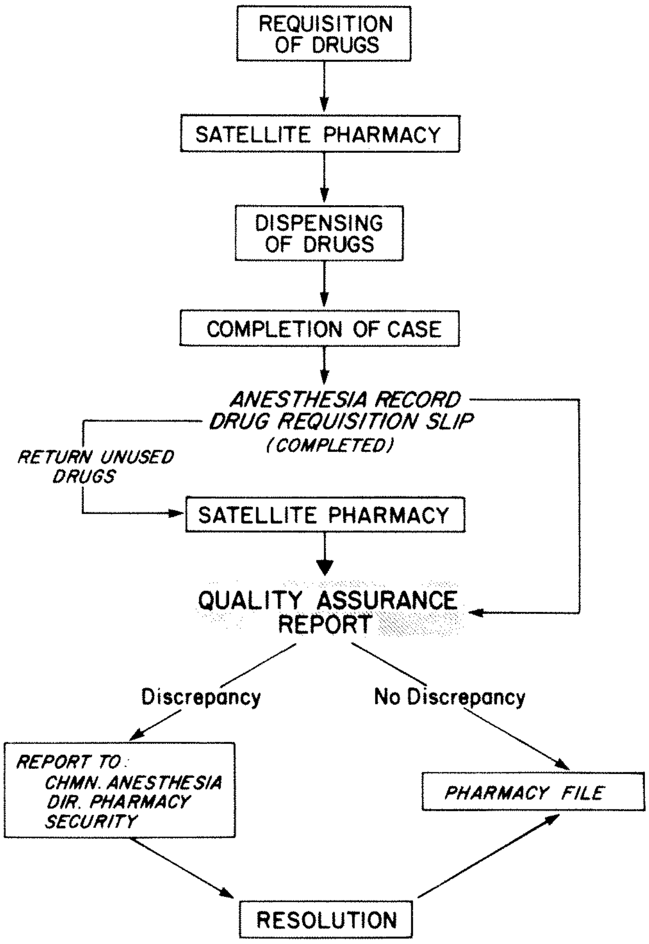
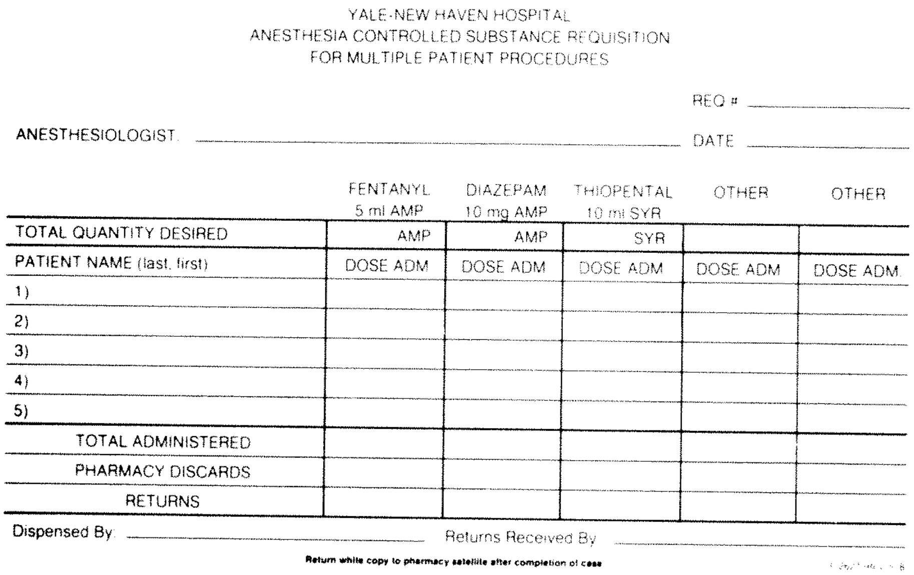


Figure 1. Controlled substance distribution flow chart.

## System during Elective Schedule

The distribution system employed at Yale–New Haven Hospital is depicted in Figure 1. Before each case or series of cases, anesthesiologists or nurse anesthetists report to the satellite pharmacy and complete and sign a requisition form for medications that are required (Fig. 2). The requisition requires basic information, including the name of the anesthesiologist, the date, and the type and amount of medication requested. The form also contains space for patient names, the amount of drug(s) actually administered to each patient and the quantity of drug(s) wasted or returned to the satellite at the completion of the case.



YALE-NEW HAVEN HOSPITAL
ANESTHESIA CONTROLLED SUBSTANCE REQUISITION
FOR MULTIPLE PATIENT PROCEDURES

REQ # ______

ANESTHESIOLOGIST ______ DATE ______

| | FENTANYL 5 ml AMP | DIAZEPAM 10 mg AMP | THIOPENTAL 10 ml SYR | OTHER | OTHER |
|---|---|---|---|---|---|
| TOTAL QUANTITY DESIRED | AMP | AMP | SYR | | |
| PATIENT NAME (last, first) | DOSE ADM | DOSE ADM | DOSE ADM | DOSE ADM | DOSE ADM |
| 1) | | | | | |
| 2) | | | | | |
| 3) | | | | | |
| 4) | | | | | |
| 5) | | | | | |
| TOTAL ADMINISTERED | | | | | |
| PHARMACY DISCARDS | | | | | |
| RETURNS | | | | | |

Dispensed By ______ Returns Received By ______

**Return white copy to pharmacy satellite after completion of case**

Figure 2. Controlled substance requisition form.

After the requisition is completed, the pharmacy technician distributes the requested drugs to the anesthesiologist with the original copy of the requisition, retaining a copy in the satellite.

Anesthesiology personnel are responsible for recording, at the completion of the operation, the quantity of drug(s) actually administered intraoperatively to each patient. This information is in addition to information recorded on the anesthesia record. At the completion of a case or at the end of the day, the completed form is returned to the satellite along with medications not used (including partially filled syringes, as well as intact units). The pharmacy technician then verifies that the sum of the amount used and the amount returned equals the original quantity requested and given to the anesthesiologist. At this time, the copy of the requisition form is discarded. Copies remaining at the end of the day indicate that drugs and requisitions are still outstanding, and the appropriate anesthesiologist is then contacted.

A complete record of disbursement and a perpetual inventory is maintained for each drug item by the pharmacy technician. A record of waste and discard of all partially used vials and syringes is also maintained, and all partial doses are discarded by the technician and a pharmacist at the end of each day.

## System during Nights and Weekends

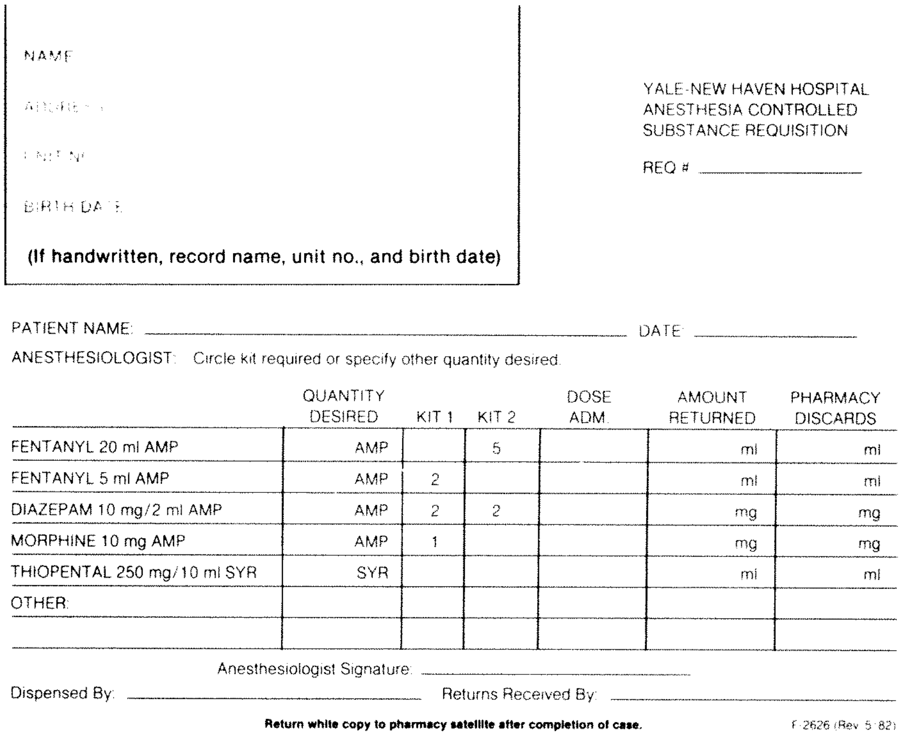
Because it would not have been cost-effective to provide a pharmacy technician 24 hr per day, a medication "night kit" system was designed to accommodate needs of the emergency schedule (3:30 PM–7 AM). Two kit types were prepared (Table 3). Kit 1, the standard kit, covers most emergency procedures. Kit 2 is provided for emergency cardiac operations. This night kit system has been extremely well received and rarely is there a need for requesting additional items not contained in these kits. Should such a need arise, additional drug items (e.g., meperidine, pentobarbital) may be requisitioned from the nursing station in the cardiothoracic intensive care unit, located adjacent to the OR complex. (In the two years since this system was instituted, fewer than ten requests for drugs have been made to the cardiothoracic ICU.)

Table 3. Night Kits

| Kit 1—Standard | | Kit 2—Open Heart | |
|---|---|---|---|
| Item | Quantity | Item | Quantity |
| Fentanyl ampuls (5 ml) | 2 | Fentanyl ampuls (20 ml) | 5 |
| Diazepam ampuls (10 mg) | 2 | Diazepam ampuls (10 mg) | 2 |
| Morphine sulfate ampul (10 mg) | 1 | | |

Kits are packaged in serially numbered zip-lock plastic bags that contain the above medications and a requisition form.

Night kits are stored in a double-locked narcotic cabinet located in the anesthesia workroom. Thiopental, which is premixed by the pharmacy department, must be refrigerated and is stored in a locked refrigerator, also located in the anesthesia workroom. Twenty standard kits, six open-heart kits, and 80 thiopental syringes are stocked in the workroom and are sufficient for a weekend (average 15 cases/weekend).



NAME

ADDRESS

UNIT NO

BIRTH DATE

**(If handwritten, record name, unit no., and birth date)**

YALE-NEW HAVEN HOSPITAL
ANESTHESIA CONTROLLED
SUBSTANCE REQUISITION

REQ # ____________

PATIENT NAME: ____________________ DATE: ____________

ANESTHESIOLOGIST: Circle kit required or specify other quantity desired.

| | QUANTITY DESIRED | KIT 1 | KIT 2 | DOSE ADM. | AMOUNT RETURNED | PHARMACY DISCARDS |
|---|---|---|---|---|---|---|
| FENTANYL 20 ml AMP | AMP | | 5 | | ml | ml |
| FENTANYL 5 ml AMP | AMP | 2 | | | ml | ml |
| DIAZEPAM 10 mg/2 ml AMP | AMP | 2 | 2 | | mg | mg |
| MORPHINE 10 mg AMP | AMP | 1 | | | mg | mg |
| THIOPENTAL 250 mg/10 ml SYR | SYR | | | | ml | ml |
| OTHER: | | | | | | |
| | | | | | | |

Anesthesiologist Signature: ____________

Dispensed By: ____________ Returns Received By: ____________

**Return white copy to pharmacy satellite after completion of case.**

F 2626 (Rev 5 82)

Figure 3. Night kit requisition form.

Only on long holiday weekends is it necessary to increase the number of kits. At the end of each regular 7:00 AM–3:30 PM shift, the pharmacy technician and the evening OR charge nurse verify the number of kits and number of thiopental syringes in the workroom, and both sign the change-of-shift record. At this time, the keys to the night cabinet and refrigerator are given to the evening charge nurse by the pharmacy technician. At each subsequent shift change, the remaining kits are verified by the charge nurses and the keys are transferred, according to state and Federal law. The nurses are responsible only for security of the keys. Record keeping is the sole responsibility of anesthesiology personnel.

When a kit is required, the charge nurse is paged to open the night cabinet. The anesthesiologist selects the kit required and signs the numbered requisition contained in the kit. The copy of this requisition is returned to the cabinet, and the original is retained by the anesthesiologist (Fig. 3). Each night kit and requisition bears a matching serial number that is also listed on a master sign-out sheet. The anesthesiologist must also sign this sheet by the appropriate number.

The night kit requisition requires the same documentation of drug usage as that used during regular hours. At the completion of the procedure, the completed requisition and any remaining drugs are placed in a plastic zip-lock bag and deposited in the return cabinet located in the holding area. This cabinet, similar to a mailbox, has a slot cut into the front doors for deposit of kits. Anesthesiology staff have been discouraged from carrying leftover quantities of controlled substances during the evening. The return box enables compliance with this policy. The pharmacy technician documents and verifies the returned kits during the next regular shift and replaces the supply of kits in the night cabinet.

## Accountability and Quality Assurance

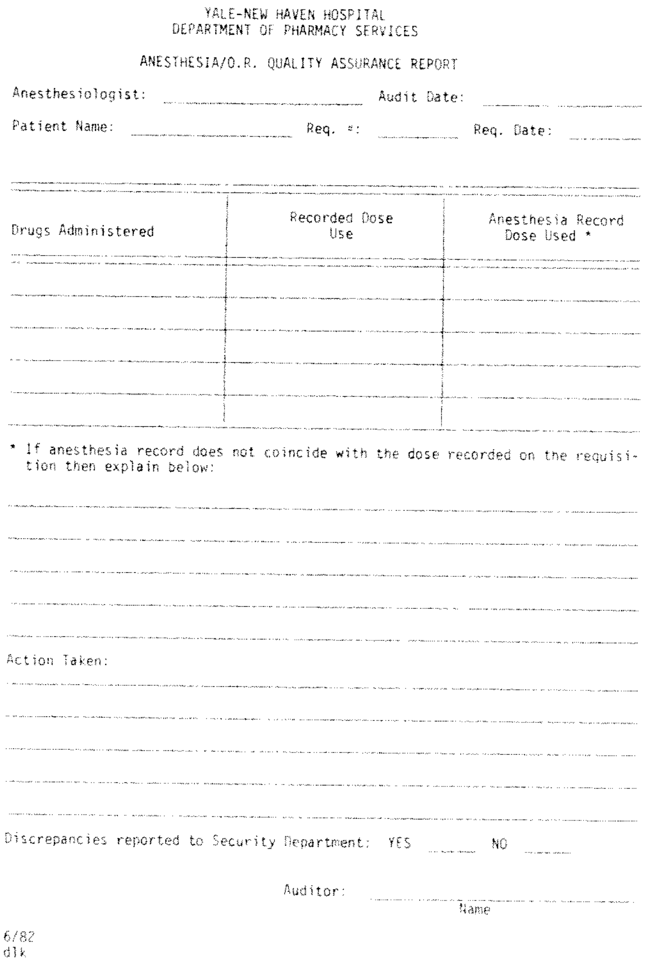
The success of any system is dependent upon the accountability of the personnel working within that system. When the new distribution system was first implemented, there was, as might be expected, some resistance by anesthesiology staff. The staff had become accustomed to the former system, which placed very little responsibility on them. It quickly became apparent that the new system would fail unless anesthesia personnel were totally accountable for their utilization of controlled substances. A strict quality assurance program was designed to provide this accountability.

Whenever a discrepancy arises (i.e., missing drugs, or missing or incomplete records), the anesthesiologist who initially requested the drugs is contacted (within 12 hr) and is asked to explain and correct the discrepancy. If the discrepancy cannot be adequately explained, the anesthesiologist is required to meet with the Chief of Anesthesiology and a hospital security officer. If the discrepancy still cannot be resolved, a written report is filed with the Security Department, and depending on the circumstances of the case, further action may be taken. This component of the quality assurance (QA) program is put into effect on a daily basis as requisitions and medications are returned to the satellite. This phase of the program ensures that the documentation of medication usage on the requisition is complete.

A second component of the QA program examines the completed requisitions and compares them to the anesthesia records. At varying times each month, 10 completed requisitions are selected at random. The anesthesia records for the patients recorded on those requisitions are then obtained and compared to the requisition. Specifically, the "amount administered" as recorded on the requisition is compared to the anesthesia record. All data are recorded on an Anesthesia/OR Quality Assurance Report Form (Fig. 4). If discrepancies exist, they are noted on the form, and copies of the form are forwarded to the Chief of Anesthesiology and the Security Department for investigation.

More recently, a third component of the QA program has been adopted. Previously, when partially used syringes and vials were returned, there was no system to verify their contents. Fentanyl, morphine, and cocaine solution are of most concern in this regard. Presently, samples of returned substances are selected at random and submitted to the hospital chemistry department or an outside laboratory for qualitative and quantitative analysis. If the analysis reveals deviation in concentration or the substance itself, this is reported to Security and an investigation is conducted.

All of the quality assurance components are well known to the OR staff, which encourages compliance. The greatest number of discrepancies occurred during the first several months after implementation of the new system. In almost all instances, the discrepancies were due to inadequacies in record keeping and documentation of drug usage data. However, in a small number of cases, discrepancies were unresolved after investigation, and this was made a matter of record and reported to the Drug Control Division, Department of Consumer Protection of the State of Connecticut.



YALE-NEW HAVEN HOSPITAL
DEPARTMENT OF PHARMACY SERVICES

ANESTHESIA/O.R. QUALITY ASSURANCE REPORT

Anesthesiologist: ________ Audit Date: ________

Patient Name: ________ Req. #: ________ Req. Date: ________

| Drugs Administered | Recorded Dose Use | Anesthesia Record Dose Used * |
|---|---|---|
| | | |
| | | |
| | | |
| | | |
| | | |

* If anesthesia record does not coincide with the dose recorded on the requisition then explain below:

Action Taken:

Discrepancies reported to Security Department: YES ____ NO ____

Auditor: ________
Name

6/82
dlk

Figure 4. Quality assurance report form.

Consistent and rapid follow-up of all discrepancies has been the key to the success of this program. The program is now well accepted by all operating room personnel. A major requirement was that the system not hamper clinical care. It has not. The advantages afforded by the system are several. The accuracy and completeness of the anesthesia record have improved considerably. The amount of medications wasted has decreased. The burden of responsibility and accountability for controlled substance use has been placed upon the personnel actually administering the drugs.

The pharmacy technician, as mentioned above, also assists in the distribution and control of other drug items in the OR. The number of missing drugs and lost charges have decreased since the inception of the system. In addition, the technician, by keeping appropriate inventory, has all but eliminated the occurrence of out-of-stock situations.

Finally, the opportunity for diversion of controlled substances in the operating room has been greatly reduced. During the first year of the program, several individuals were involved in unexplained discrepancies that resulted in investigations and appropriate actions. However, during the last two years, no documented discrepancies have occurred. In a number of instances, discrepancies have been due to record keeping errors or illegible handwriting. Individuals initially suspected of drug diversion because of unusual prescribing profiles, have been subsequently exonerated following further investigation.

If the incidence of chemical impairment is more prevalent in operating room personnel, the ready availability of these substances may well be the major contributing factor (6). No drug control system is tamper-proof. However, the system utilizing a pharmacy satellite in the OR area makes drug diversion considerably more difficult and increases the probability of detection. In an effort to further improve the system, plans are being made to develop routine review of drug-administration profiles. This profile would not only review average controlled substance utilization by individual anesthesiologists, nurses, and surgeons, but will also create an "average use profile" for each year of the anesthesia residency program. Significant deviation from the normal use profile would warrant further investigation.*

The operating room pharmacy satellite can provide increased control and accountability of controlled substance use. The program is a multidisciplinary one and should involve a cooperative effort by the Departments of Anesthesiology, Pharmacy, Security, and Nursing in order to maximize its benefits. The program does not impede clinical care and does not require an increased time commitment by OR personnel. The key to the success of this, or similar programs, is the inclusion of a quality assurance component that provides an absolute audit trail of medication use.

The authors wish to acknowledge an educational grant by Janssen Pharmaceutica.

## References

1. Thomas RB, Luber SA, Smith JA. A survey of alcohol and drug use in medical students. Dis Nerv Sys 1977;38:41–3.
2. Hall RCW, Stickney SK, Popkin MK. Physician drug abuser. J Nerv Ment Dis 1978;166:787–93.
3. Talbott GD, Benson EF. Impaired physician: the dilemma of identification. Postgrad Med 1980;68:56–64.
4. Johnson RP, Connelly JC. Addicted physicians: a closer look. JAMA 1981;245:253–7.
5. Herrington RE, Benzer DG, Jacobson GR, et al. Treating substance-use disorders among physicians. JAMA 1982;247:2253–7.
6. Ward CF, Ward GC, Saidman LJ. Drug abuse in anesthesia training programs. JAMA 1983;250:922–5.
7. Evans DM, Duenther AM, Keith TD, et al. Pharmacy practice in an operating room complex. Am J Hosp Pharm 1979;36:1342–7.
8. McClure-Zola E, Cipolle RJ, Zaske DE. Distribution system for controlled substances in the operating room. Am J Hosp Pharm 1981;38:687–9.
9. Powell PJ, Maland L, Bair JN, et al. Implementing an operating room pharmacy satellite. Am J Hosp Pharm 1983;40:1192–8.

## *Note Added in Proof

Since we submitted this paper, Adler et al. have published a discussion of the use of a computer-generated report of individual drug usage trends by anesthesiologists: Adler GR, Potts FE III, Kirby RR, et al. Narcotics control in anesthesia training. JAMA 1985;258:3133–6.

ANESTH ANALG
1985;64:996–1000

# Comparison of the Effects of General and Regional Anesthesia for Cesarean Section on Neonatal Neurologic and Adaptive Capacity Scores

Therese K. Abboud, MD, Shakuntala Nagappala, MD, Kazushige Murakawa, MD, Saul David, MD, Sarkis Haroutunian, MD, Makrouhi Zakarian, MD, Thormason Yanagi, MD, and Amir Sheikh-Ol-Eslam, MD

ABBOUD TK, NAGAPPALA S, MURAKAWA K, DAVID S, HAROUTUNIAN S, ZAKARIAN M, YANAGI T, SHEIKH-OL-ESLAM A. Comparison of the effects of general and regional anesthesia for cesarean section on neonatal neurologic and adaptive capacity scores. Anesth Analg 1985;64:996–1000.

*Fifty-two neonates delivered by elective cesarean section were evaluated using the Neonatal Neurologic and Adaptive Capacity Scores. Twenty of the mothers received general anesthesia, 14 received epidural, and 18 received spinal anesthesia. All mothers receiving regional anesthesia were prehydrated with 1000 ml of lactated Ringer's solution and were given oxygen via a transparent face mask. All mothers undergoing general anesthesia received thiopental for induction followed by* $N_2O$–$O_2$ *(4 L:4 L) and 0.5% enflurane until delivery of the baby. All mothers were healthy, not in labor, and were scheduled for elective cesarean section. All neonates weighed 2500 g or more, had Apgar scores of 7 or more at 1 and 5 min, and had normal acid base and blood gas data. Neonates delivered with general anesthesia scored significantly lower on some of the test items for adaptive capacity, passive tone, active tone, primary reflexes, and total scores at both 15 min and 2 hr of age (*$P < 0.05$*) than those delivered with either epidural or spinal anesthesia. Neonates delivered with epidural anesthesia scored lower than those delivered with spinal anesthesia on supporting reaction and motor activity at 2 hr of age (*$P < 0.05$*). All neonates had high scores at 24 hr, at which time there were no significant differences between the three groups.*

Key Words: ANESTHESIA, OBSTETRIC.

Traditionally, neonatal condition at delivery has been evaluated clinically with the Apgar scoring system and biochemically with umbilical cord acid–base measurements. Although both are immensely useful in detecting gross neonatal drug depression, perinatal trauma, and birth asphyxia, these tests evaluate only depression of vital functions and are insensitive to subtle or delayed effects. Many infants may show alterations in neurologic and behavioral function despite normal or high Apgar scores (1–4).

Neurobehavioral tests include the Scanlon Early Neonatal Neurobehavioral Scale (ENNS) (5) and, most recently, the Amiel-Tison/Barrier/Shnider Neurological and Adaptive Capacity Score (NACS) (6). These examinations differ in their comprehensiveness and the emphasis they place on the various aspects of neurologic function and newborn behavior.

NACS is a test that is easy to perform and score. It also places special emphasis on tests designed to evaluate passive tone. To date there have been no reports in which NACS detected adverse neonatal responses to anesthesia. The present study was undertaken to evaluate the validity and the sensitivity of the NACS examination and also to compare the effects of general and regional anesthesia for cesarean section on neonatal neurobehavioral performance.

## Materials and Methods

Fifty-two healthy women at term, not in labor, and scheduled for elective cesarean section volunteered to participate in the study. Informed consents were obtained from all patients after approval by the Human Research Committee of Los Angeles County-University of Southern California Medical Center. None of the patients received any narcotics or sedatives prior to anesthetic induction. Patients were divided into three groups: group 1 patients ($n = 20$) received general anesthesia, group 2 patients ($n = 18$) received

---

Received from the Department of Anesthesiology, Los Angeles County-University of Southern California Medical Center, Los Angeles, California. Accepted for publication February 7, 1985.

Address correspondence to Dr. Abboud, Box 12, LAC-USC Medical Center, 1200 North State Street, Los Angeles, CA 90033.

© 1985 by the International Anesthesia Research Society

Table 1. Patient Data

| | Group 1 ($n = 20$) General | Group 2 ($n = 18$) Spinal | Group 3 ($n = 14$) Epidural |
|---|---|---|---|
| Maternal age (yr) | 29.4 ± 1.6 | 27.9 ± 1.2 | 28.2 ± 1.1 |
| Maternal height (cm) | 158.0 ± 4.3 | 161.2 ± 5.5 | 157.4 ± 8.6 |
| Maternal weight (kg) | 61.4 ± 0.7 | 62.2 ± 0.8 | 61.7 ± 0.6 |
| Gestational age (wk) | 38.4 ± 0.7 | 39.5 ± 0.3 | 39.8 ± 0.4 |
| Infant weight (g) | 3508 ± 128 | 3634 ± 65 | 3430 ± 104 |

Values are mean ± SEM. No significant differences between groups by Student's *t*-test.

Table 2. Acid-Base and Blood-Gas Data

| | Group 1 General | Group 2 Spinal | Group 3 Epidural |
|---|---|---|---|
| Umbilical vein | | | |
| Number | 20 | 18 | 14 |
| pH | 7.33 ± 0.01 | 7.32 ± 0.01 | 7.33 ± 0.01 |
| $PO_2$ (torr) | 27.1 ± 2.4 | 26.8 ± 1.9 | 24.0 ± 1.2 |
| $PCO_2$ (torr) | 41.0 ± 1.8 | 40.7 ± 1.5 | 38.6 ± 1.3 |
| Base excess (mEg/L) | −3.8 ± 0.5 | −4.6 ± 0.5 | −4.3 ± 0.7 |
| Umbilical artery | | | |
| Number | 20 | 18 | 13 |
| pH | 7.28 ± 0.01 | 7.25 ± 0.02 | 7.27 ± 0.01 |
| $PO_2$ | 16.5 ± 1.1 | 14.0 ± 0.9 | 14.2 ± 1.1 |
| $PCO_2$ | 48 ± 2.0 | 51.7 ± 2.0 | 48.0 ± 1.1 |
| Base excess (mEq/L) | −2.8 ± 0.4 | −3.7 ± 0.4 | −3.5 ± 0.4 |

Values are mean ± SEM. No significant differences between groups as determined by Student's *t*-test.

spinal anesthesia, and group 3 patients ($n = 14$) received epidural anesthesia. Group 1 patients were premedicated with 0.2 mg glycopyrrolate intravenously and a clear oral antacid. After 3 mg *d*-tubocurarine, anesthesia was induced using thiopental 4 mg/kg followed by succinylcholine 1.5 mg/kg, and endotracheal intubation. Anesthesia was maintained with nitrous oxide, oxygen (4 L:4 L), and 0.5% enflurane until delivery of the infant. Enflurane was discontinued after delivery of the infant and intermittent increments of 2 mg of butorphanol were then given intravenously to supplement $N_2O$. Ventilation was controlled using a mechanical ventilator. Before administration of the regional anesthetic, all patients received 1000 ml of lactated Ringer's solution. Spinal anesthesia was performed at the level of $L_3$–$L_4$ interspace using 1% tetracaine with an equal volume of 10% dextrose and epinephrine with doses of tetracaine ranging from 7–8 mg. Epidural anesthesia was administered through an epidural catheter placed at the $L_3$–$L_4$ interspace using either 3% 2-chloroprocaine ($n = 7$) or 2% lidocaine ($n = 7$), both with 1:200,000 epinephrine. Initial volumes of 15–20 ml of local anesthetics were used. All patients in groups 2 and 3 received oxygen via a face mask after administration of the regional anesthesia. Left uterine displacement was maintained in all patients in all groups.

NACS scores in the 52 neonates were assessed at 15 min, 2 hr, and 24 hr of age. All neonates weighed 2500 g or more, had Apgar scores of 7 or more at 1 and 5 min, and had normal acid–base and blood gas data. The NACS was performed by an anesthesia research fellow trained to perform this examination by the senior author who had been trained by Dr. Shnider. The NACS gives a total score, the maximum being 40. Arbitrarily choosing 35–40 as the score denoting a vigorous baby (6,15), we determined the percentage of infants scoring 35 or higher and compared these in the three groups at 15 min, 2 hr, and 24 hr. We also determined the percentage of infants having high scores on each of the individual test items i.e., those having scores of 2.

Data were analyzed for statistical significance using Student's *t*-test and $\chi$-square when appropriate. A $P$ value of $< 0.05$ was considered statistically significant.

## Results

Data on maternal age, weight, height, infant gestational age, and weight are summarized in Table 1. There were no significant differences among the three groups. All neonates had normal blood gas and acid–base status, and there were no significant differences between the three groups (Table 2).

NACS scores did not differ significantly between the neonates whose mothers received epidural lidocaine and those who received chloroprocaine; for this reason the data for the epidural group were pooled.

Neonates delivered with general anesthesia scored significantly lower than did neonates delivered with either epidural or spinal anesthesia in tests of adaptive capacity, passive tone, active tone, primary reflexes, and total scores at both 15 min and 2 hr of age. Neonates delivered with epidural anesthesia scored significantly lower than those delivered with spinal anesthesia in tests of supporting reaction and motor activity at 2 hr, but there were no differences at 15 min of age. All neonates had high scores at 24 hr at which time there were no significant differences between the 3 groups (Table 3).

Table 3. Percentage of Infants who Scored 2 for Each Test Item of the Neurologic and Adaptive Capacity Score after Cesarean Section Using General Anesthesia (Group 1), Spinal Anesthesia (Group 2) or Epidural Anesthesia (Group 3)

| | 15 min | | | 2 hr | | | 24 hr | | |
|---|---|---|---|---|---|---|---|---|---|
| Groups | 1 | 2 | 3 | 1 | 2 | 3 | 1 | 2 | 3 |
| Adaptive capacity | | | | | | | | | |
| Sound | 47 | 50 | 43 | 40 | 89[b] | 62 | 75 | 100 | 85 |
| Habituation to sound | 45 | 44 | 36 | 67 | 56 | 82 | 65 | 81 | 69 |
| Light | 85 | 89 | 93 | 83 | 89 | 92 | 90 | 87 | 92 |
| Habituation to light | 60 | 72 | 57 | 72 | 67 | 89 | 85 | 81 | 77 |
| Consolability | 80 | 100 | 93 | 94 | 100 | 92 | 100 | 100 | 100 |
| Passive tone | | | | | | | | | |
| Scarf sign | 80 | 94 | 86 | 95 | 100 | 85 | 100 | 94 | 92 |
| Elbow recoil | 40 | 89 | 93[a] | 50 | 100[b] | 92 | 85 | 87 | 100 |
| Lower limb recoil | 85 | 94 | 100 | 89 | 100 | 100 | 95 | 94 | 100 |
| Popliteal angle | 90 | 100 | 100 | 95 | 100 | 100 | 95 | 94 | 100 |
| Active tone | | | | | | | | | |
| Neck flexors | 70 | 78 | 79 | 94 | 94 | 92 | 95 | 94 | 92 |
| Neck extensors | 70 | 89 | 79 | 78 | 94 | 85 | 85 | 100 | 92 |
| Palmar traction | 35 | 67 | 93[a] | 72 | 72 | 67 | 80 | 75 | 69 |
| Supporting reaction | 80 | 100 | 89 | 89 | 100[c] | 69 | 95 | 100 | 92 |
| Primary reflexes | | | | | | | | | |
| Palmar grasp | 60 | 83 | 71 | 83 | 83 | 54 | 85 | 87 | 69 |
| Automatic walking | 40 | 61 | 93[a] | 56 | 67 | 77 | 60 | 63 | 62 |
| Sucking | 90 | 89 | 79 | 100 | 100 | 100 | 100 | 100 | 100 |
| Motor response | 100 | 100 | 100 | 94 | 100 | 100 | 100 | 100 | 100 |
| General assessment | | | | | | | | | |
| Alertness | 95 | 100 | 93 | 94 | 100 | 86 | 95 | 100 | 100 |
| Crying | 100 | 100 | 93 | 94 | 100 | 85 | 100 | 100 | 92 |
| Motor activity | 80 | 100 | 86 | 89 | 100[c] | 69 | 90 | 100 | 100 |
| % of good scores on all tests | 45 | 78 | 93[c] | 94 | 94 | 77 | 95 | 100 | 92 |

[a] Statistically significant differences between general and epidural anesthesia.
[b] Statistically significant differences between general and spinal anesthesia.
[c] Statistically significant differences between spinal and epidural.

## Discussion

Findings from the present study indicate that general anesthesia for cesarean section is more depressant than regional anesthesia on NACS. They also indicate that the NACS examination is a valid and sensitive test for evaluating neurobehavioral performance scores. Hodgkinson et al. (3) have also found that babies delivered after general anesthesia for cesarean section scored lower than those delivered after spinal anesthesia, using the Early Neonatal Neurobehavioral Scores.

The ENNS has been used primarily to examine neurobehavioral changes associated with the use of anesthetic drugs. The test was designed to be performed 2–8 hr after birth, a time that corresponds to the neonatal half-life of commonly used amide local anesthetics. Anesthetic-related neurobehavioral changes were primarily manifested as decreased tone or diminished response decrement in an otherwise alert infant (5).

The NACS developed by Amiel-Tison et al. embodies some portions of the Brazelton Neonatal Behavioral Assessment Scale (7), the Scanlon ENNS (5), and the Amiel-Tison neurologic examination (8). All criteria were chosen from those used in standard neurologic and clinical behavioral testing. They specifically chose items that have been demonstrated to be affected by obstetric medications, perinatal asphyxia, or birth trauma. Like Scanlon, they also selected specific items that were easy to perform, required no complicated equipment, were quickly observable and simple to score, and possessed a high interobserver reliability. However, Amiel-Tison et al. (6) believed that the ENNS puts too little emphasis on neonatal tone, and is not designed to distinguish tone differences in extensor and flexor muscles of the neck or differences in tone between upper and lower parts of the body. They believe that these differentiations are important in diagnosing abnormalities that are due to birth trauma rather than to drug depression. The ENNS also uses strongly aversive stimuli, such as repeated pinprick and Moro maneuver that are a potential source of maternal hostility when the newborn infant is tested in the presence of the mother.

Finally, the NACS uses eight separate tests for tone.

Four tests of passive tone emphasize the upper and lower extremities equally, and allow detection of hypotonia that may be unilateral or confined to the upper part of the body, as seen in mild birth trauma or perinatal asphyxia (8). The same is true for the tests of active tone. Additionally, the tests of active tone are more refined, which allows detection of abnormally high tone in neck extensors, as occurs in intracranial hypertension (9). Generalized mediocre tone responses probably indicate a more global depression and are frequently associated with drugs and anesthetics.

Other reports have also shown that general anesthesia for vaginal delivery was associated with lower neurobehavioral scores than regional anesthesia (2), possibly due to thiopental, which might depress the neonate due to its slow rate of metabolism. The medium-acting barbiturates, including pentobarbital, which is the main metabolite of thiopental, have previously been shown to depress sucking in neonates (10,11). The metabolites of thiopental also have an effect on the electroencephalogram of neonates for several days (12). Because the importance of neonatal neurobehavioral tests is still unknown, it would seem reasonable to assume that a high-risk neonate may be more likely to do well with regional anesthesia than with general anesthesia since tone and reflexes are better with regional anesthesia, but further work is needed to fully evaluate this issue. Another advantage of regional anesthesia over general anesthesia in obstetrics is the parent–child bonding (13,14), which can be adversely affected by obstetric medications.

In the present study neonates delivered after epidural anesthesia scored lower than those delivered after spinal anesthesia for motor activity and supporting reaction at 2 hr, but not at 15 min of age. Since no apparent explanation for this difference is available, the smaller amounts of local anesthetics used for spinal anesthesia might have been a factor in accounting for this difference. Other reports have also shown that neurobehavioral test performance decreaces at 2–4 hr of age (15,16). KLaus and Kennel (17), and Desmond et al. (18) report that after birth there is a 45–60 min period of infant alertness or "reactivity" that is followed by a 3 or 4 hr interval of deep sleep and poor responsiveness. Another period of alertness then occurs. Therefore any test of neurobehavioral status performed 2–4 hr after birth probably would find the infant less responsive and would reveal decreased neonatal performance.

It is concluded from our study that the NACS that has been used recently to evaluate neonatal effects of obstetric medications (15,19–21) is a valid and sensitive examination for neurobehavioral performance, and that general anesthesia for cesarean section is more depressant than regional anesthesia during the first few hours of life. Because these findings may have minimal effects on a healthy infant, a high risk neonate may be adversely affected by general anesthesia and further work is needed to evaluate the effect of general and regional anesthesia on high risk neonates.

## References

1. Brackbill Y, Kane J, Manniello RL, Abramson D. Obstetric premedication and infant outcome. Am J Obstet Gynecol 1974;118:377–9.
2. Hodgkinson R, Marx GF, Kim SS, Miclat NM. Neonatal neurobehavioral tests following vaginal delivery under ketamine, thiopental and extradural anesthesia. Anesth Analg 1977;56:548–53.
3. Hodgkinson R, Bhatt M, Kim SS, Grewal G, Marx GF. Neonatal neurobehavioral tests following cesarean section under general and spinal anesthesia. Am J Obstet Gynecol 1978;132:670–4.
4. Hodgkinson R, Bhatt M, Grewal G, Marx GF. Neonatal neurobehavior in the first 48 hours of life: effect of the administration of meperidine with and without naloxone in the mother. Pediatrics 1978;62:294–8.
5. Scanlon JW, Brown MU, Weiss JB, Alper MH. Neurobehavioral responses of newborn in infants after maternal epidural anesthesia. Anesthesiology 1974;40:121–8.
6. Amiel-Tison C, Barrier G, Shnider SM, Levinson G, Hughes SC, Stephani SJ. A new neurologic and adaptive capacity scoring system for evaluating obstetric medications in full-term newborns. Anesthesiology 1982;56:340–50.
7. Brazelton TB. Neonatal Behavioral Assessment Scale. Clinics in Developmental Medicine No. 50. Spastics International Medical Publications. London: William Heinemann Medical Books Ltd, 1973.
8. Amiel-Tison C. A method for neurological evaluation within the first year of life: experience with full-term newborn infants with birth injury. Major Mental Handicap: Methods and Costs of Prevention, Ciba Foundation Symposium 59. Amsterdam: Elsevier/Excerpta Medica/North-Holland, 1978:107–26.
9. Amiel-Tison C, Korobkin R, Esque-Vaucouloux MT. Neck extensor hypertonial: a clinical sign of insult to the central nervous system of the newborn. Early Hum Dev 1977;1:181–90.
10. Brazelton TB. Psychologic reactions in the neonate. II. Effects of maternal medication on the neonate and his behavior. J Pediatr 1961;58:513–18.
11. Kron RE, Stein M, Goddard KE. Newborn sucking behavior affected by obstetric sedation. Am J Psychiatry 1966;37:1012.
12. Hughes JG, Ehemann B, Brown UA. Electroencephalography of the newborn. III. Brain potentials of babies born of mothers given seconal sodium. Am J Dis Child 1948;76:626–33.
13. Brazelton TB. The effect of prenatal drugs on the behavior of the neonate. Am J Psychiatry 1970;126:95–100.
14. Klaus MH, Kennel JH, Plumb N, Zuehlke S. Human maternal behavior at the first contact with her young. Pediatrics 1970;46:187–92.
15. Stephani SJ, Hughes SC, Shnider SM, et al. Neonatal neurobehavioral effects of inhalation analgesia for vaginal delivery. Anesthesiology 1982;56:351–5.
16. McGuinness GA, Merkow AJ, Kennedy RL, et al. Epidural anesthesia with bupivacaine for cesarean section: neonatal blood levels and neurobehavioral responses. Anesthesiology 1978;49:270–3.

# Intracranial Pressure During Diltiazem-induced Hypotension in Anesthetized Dogs

Paul Mazzoni, MD, Joseph P. Giffin, MD, James E. Cottrell, MD, John Hartung, PhD, Christine Capuano, BS, and Jeffrey M. Epstein, MD

MAZZONI P, GIFFIN JP, COTTRELL JE, HARTUNG J, CAPUANO C, EPSTEIN JM. Intracranial pressure during diltiazem-induced hypotension in anesthetized dogs. Anesth Analg 1985;64:1001–4.

*The effect of diltiazem-induced hypotension on intracranial pressure (ICP) was studied in dogs with normal and elevated ICP. Eight dogs were anesthetized with intravenous pentobarbital, intubated, and ventilated with $N_2O$:$O_2$. Mean arterial pressure (MAP), heart rate (HR), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), and cardiac output (CO) were recorded. A ventriculostomy was performed for measurement of ICP. Baselines were established, and diltiazem was infused to reduce MAP 40 ± 1% for 10 min. After recording the effects of diltiazem-induced hypotension during normal ICP, ICP was elevated by infusion through a ventriculostomy cannula of pH-adjusted Ringer's lactate, baselines were reestablished, and MAP was again reduced by 40 ± 1% with diltiazem. When baseline ICP was normal, diltiazem-induced hypotension produced a statistically significant increase in ICP (4.8 ± 0.6 mm Hg) and a decrease in cerebral perfusion pressure (CPP). When baseline ICP was elevated, a smaller increase in ICP occurred (1.3 ± 0.5 mm Hg). Although these increases in ICP were not clinically significant, the dose of diltiazem required to lower MAP 40% caused significant alterations in HR, systemic vascular resistance, CO, and PCWP. Serious cardiac rhythm disturbances occurred in five of eight dogs when baseline ICP was normal and in six of eight dogs when baseline ICP was elevated. The relatively long duration of diltiazem's hemodynamic effect and the high incidence of cardiac rhythm disturbances make it an unsuitable drug for inducing deliberate hypotension.*

Key Words: BRAIN—intracranial pressure. PHARMACOLOGY—diltiazem.

Drugs currently available for inducing hypotension either increase intracranial pressure (ICP), are potentially toxic, or have toxic metabolites (1). When mass lesions compromise intracranial compliance, a sudden increase in ICP associated with a decrease in mean arterial pressure (MAP) may lower cerebral perfusion pressure (CPP) to less than 40 mm Hg, resulting in cerebral ischemia (2).

Three calcium entry blocking drugs are currently available for clinical use in the United States. They are systemic arterial vasodilators and potent cerebral artery vasodilators (3). Calcium channel blockers have been shown to be effective spasmolytic agents (4), and two of these drugs, nifedipine and verapamil, have been reported to increase ICP in doses that significantly decrease blood pressure (5,6). The effect of diltiazem on ICP is unknown. Therefore, we investigated the effects of diltiazem-induced hypotension on ICP in dogs with normal and elevated ICP.

## Materials and Methods

Eight mongrel dogs (15–21 kg) were anesthetized with acepromazine (1 mg) and intravenous pentobarbital (10–12 mg/kg), intubated, and ventilated with 70% $N_2O$ in $O_2$ to maintain arterial carbon dioxide tension ($Pa\text{CO}_2$) at 34 ± 2 mm Hg and arterial oxygen tension ($Pa\text{O}_2$) greater than 100 mm Hg. Incremental pancuronium (2 mg) was used as necessary for muscle relaxation. A femoral arterial catheter was inserted for monitoring blood pressure and sampling arterial blood, and a flow-directed thermodilution pulmonary arterial catheter was placed via the femoral vein for measurement of central venous pressure (CVP), pulmonary artery pressure (PAP), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO). Heart rate and rhythm were monitored by standard four-lead electrocardiogram (ECG). A right posterior parietal burr hole was made, and a lateral ventriculostomy cannula (20-gauge angiocatheter) was inserted for ICP

---

Received from the Departments of Anesthesiology and Neurosurgery, State University Hospital, Downstate Medical Center, Brooklyn, New York. Accepted for publication April 2, 1985.

Address correspondence to Dr. Cottrell, Department of Anesthesiology, State University Hospital, Downstate Medical Center, 450 Clarkson Avenue, Box 6, Brooklyn, NY 11203.

© 1985 by the International Anesthesia Research Society

determination. Baseline values were recorded when ICP was normal. Diltiazem (2.5 mg/ml) was then infused through a peripheral vein to lower MAP by 40 ± 1% for 10 min. ICP, ECG, CVP, and PAP were recorded continuously. CO was measured in triplicate just prior to administration of diltiazem and 1, 5, and 10 min after diltiazem. Diltiazem infusion was then discontinued, and baselines were reestablished. ICP was then increased over a 10-min period to 31 ± 1 mm Hg by infusion of pH-adjusted Ringer's lactate through the ventriculostomy cannula. Diltiazem was again infused to decrease MAP by 40%, and measurements were repeated.

We did not randomize the order of elevated vs normal ICP baseline conditions because experience has shown us that sustained elevation of ICP often causes a supercompliant condition that invalidates subsequent tests of drug effects in the presence of normal ICP. That is, if we give a known cerebral vasodilator, like nitroprusside, under the condition of initially normal ICP, we are likely to get a 10–15 mm Hg increase. However, if we check the effect of nitroprusside on normal ICP after having checked the effect on artificially elevated ICP, the effect on normal ICP is attenuated by about half. In distinction, checking the effect of a drug on normal ICP first does not, in our experience, affect the subsequent effect during elevated ICP.

For both normal and elevated ICP conditions, values of PAP, PCWP, CO, and HR used for analysis were the average of the 1-, 5-, and 10-min postdiltiazem values. ICP values used for analysis were taken at their point of maximum change between initiation of diltiazem infusion and restoration of baseline MAP. Cerebral perfusion pressure (CPP) was calculated from the formula CPP = MAP − ICP. Systemic vascular resistance (SVR) was calculated as SVR = (MAP − CVP)/CO. Results were analyzed for statistical significance using the two-tail paired *t*-test, with each animal's prediltiazem baseline serving as control. *P* values <0.05 were considered statistically significant, and all intervals reported with mean values are ± standard error of the mean (SEM).

## Results

When ICP was normal, 0.23 ± 0.04 $mg{\cdot}kg^{-1}{\cdot}min^{-1}$ of diltiazem was required to reduce MAP from 115 ± 5 mm Hg to 70 ± 4 mm Hg. When ICP was elevated, 0.20 ± 0.03 $mg{\cdot}kg^{-1}{\cdot}min^{-1}$ of diltiazem was required to reduce MAP from 107 ± 7 mm Hg to 66 ± 5 mm Hg. Onset of action was 1–2 min with recovery to near baseline (within 10%) requiring 30–60 min (average 50), with no difference in recovery time between the two initial ICP conditions.

Table 1. The Effect of Diltiazem on MAP, ICP, HR, CO, PAP, PCWP, SVR, and CPP in Dogs with Normal ICP

| | Control | Diltiazem | Mean Δ ± SEM |
|---|---|---|---|
| MAP (mm Hg) | 115 ± 5 | 70 ± 4 | 46 ± 2[b] |
| ICP (mm Hg) | 7.9 ± 0.5 | 12.6 ± 0.8[a] | 4.8 ± 0.6[b] |
| HR (beats/min) | 177 ± 6 | 131 ± 10 | 46 ± 10[b] |
| CO (L/min) | 4.8 ± 0.4 | 4.9 ± 0.4 | 0.1 ± 0.4[d] |
| PCWP (mm Hg) | 4.6 ± 0.5 | 7.1 ± 1.1 | 1.6 ± 1.0[c] |
| PAP (mm Hg) | 16 ± 1 | 17 ± 1 | 0.6 ± 1.4[d] |
| SVR[e] | 25 ± 2 | 15 ± 2 | 10 ± 1.0[b] |
| CPP (mm Hg) | 108 ± 5 | 58 ± 4 | 50 ± 2.0[b] |

All values are mean ± SEM ($n = 8$).
[a] Highest ICP after diltiazem.
[b] $P < 0.01$.
[c] $P < 0.05$.
[d] Not significant.
[e] SVR was measured in $10^2$ $dynes{\cdot}sec{\cdot}cm^{-5}$.

During diltiazem-induced hypotension, under both initial ICP conditions, statistically significant increases in ICP occurred. When initial ICP was normal, the increase was 4.8 ± 0.6 mm Hg, and CPP was reduced to 58 ± 4 mm Hg. When ICP was elevated, the increase was 1.3 ± 0.5 mm Hg, and CPP was reduced to 38 ± 3 mm Hg. Diltiazem significantly reduced HR under both initial ICP conditions. With the diltiazem doses necessary to produce a 40% decrease in MAP, serious cardiac rhythm disturbances occurred in five of eight dogs when baseline ICP was normal and in six of eight dogs when baseline ICP was elevated. These disturbances consisted of second degree atrioventricular block of the Mobitz I variety. SVR decreased significantly under both experimental conditions. CO was unaltered when ICP was normal but was reduced significantly when initial ICP was elevated. PAP remained unchanged under both ICP conditions, while PCWP increased (see Tables 1 and 2).

## Discussion

During diltiazem-induced hypotension, ICP increased in dogs with normal and elevated ICP. This result is congruent with the finding that diltiazem increases common carotid, internal carotid, and regional cerebral blood flow in dogs (4). Although both increases in ICP were statistically significant, neither increase was clinically significant. Intracranial pressure remained within the normal range, and CPP was maintained at an acceptable level. Our observed increase in ICP during diltiazem-induced hypotension was small compared to nitrate-induced arterial hypotension (7). This may be because calcium entry blockers have negligible effects on venous capacitance vessels, whereas nitrates produce marked venous dilatation (8,9). Comparison of our results with other studies suggests that diltiazem-induced hypotension

Table 2. The Effect of Diltiazem on MAP, ICP, HR, CO, PAP, PCWP, SVR and CPP in Dogs with Increased ICP

| | Control | Diltiazem | Mean Δ ± SEM |
|---|---|---|---|
| MAP (mm Hg) | 107 ± 7 | 66 ± 5 | 37 ± 1.0[b] |
| ICP (mm Hg) | 30.9 ± 0.9 | 32.1 ± 1.3[a] | 1.3 ± 0.5[c] |
| HR (beats/min) | 161 ± 10 | 110 ± 10 | 52 ± 11[b] |
| CO (L/min) | 5.5 ± 0.5 | 4.5 ± 0.5 | 1 ± 0.2[b] |
| PCWP (mm Hg) | 4.7 ± 0.4 | 8 ± 0.8 | 3.3 ± 0.6[b] |
| PAP (mm Hg) | 16 ± 1 | 17 ± 1 | 0.8 ± 0.8[d] |
| SVR[e] | 19 ± 2 | 15 ± 2 | 4 ± 0.5[b] |
| CPP (mm Hg) | 72 ± 7 | 35 ± 5 | 38 ± 3.0[b] |

All values are mean ± SEM ($n = 8$).
[a] Highest ICP after diltiazem.
[b] $P < 0.01$.
[c] $P < 0.05$.
[d] Not significant.
[e] SVR was measured in $10^2$ dynes·sec·cm$^{-5}$.

also produces smaller increases in ICP than either verapamil (6) or nifedipine (5).

We recorded a 4.8 mm Hg increase in ICP during diltiazem-induced hypotension when baseline ICP was normal, and a 1.3 mm Hg increase in ICP when baseline ICP was elevated. Although neither of these increases was clinically significant, we would have expected the larger absolute increase to occur when baseline ICP was elevated. Perhaps diltiazem's effect on relaxation of cerebral vessels was the same with both administrations, but the lesser amount of actual dilation (and so the lesser increase in ICP) occurred because control blood pressure was 8 mm Hg lower during the second administration of diltiazem (see Tables 1 and 2).

Rapid onset and termination of action are requirements of an ideal agent for induction of arterial hypotension during anesthesia. Although the onset of action of diltiazem is comparable to many commonly used hypotensive agents (1–2 min), its duration of action (average 50 min) is far longer. Indeed, comparison of control hemodynamic values for our first and second administrations of diltiazem (see Tables 1 and 2) indicates that even a 50-min wait left MAP, HR, and SVR slightly depressed. This raises the possibility that our second administration was contaminated by residual from the first. Albeit, five of the six dogs that experienced disarrhythmias during the second administration of diltiazem also suffered disarrhythmias during the first administration. Because the first administration cannot have been contaminated by the second, the empirical validity of this finding is not an artifact of cumulative effects.

In the present study, diltiazem reliably reduced MAP in dogs. As is true with other calcium entry blockers, this results predominantly from decreased SVR (10). The effect of calcium entry blockers on CO, myocardial contractility, and HR are variable and depend upon simultaneous compensatory sympathetic response to vasodilation and the negative inotropy of the drug. Cardiac output may remain unchanged, as in the initial part of our experiment (Table 1), may increase when left ventricular function is normal, or may decrease due to a predominance of negative inotropy, as occurred in the latter half of our study. Reduction in CO is not likely to occur in patients with impaired left ventricular (LV) function (11,12). Although plasma renin does significantly increase during calcium entry blocker therapy (13,14), rebound hypertension has not been reported upon discontinuation of diltiazem and was not seen in our study. Our finding that PAP remained stable is in agreement with other work finding no change in subjects with normal PAP (15,16).

Kapur and Tippit (17) recently reported prolonged PR intervals and Wenkebach heart block in dogs given less than one tenth the dose of diltiazem required to reduce MAP by 40% in our study. The majority of our animals developed atrioventricular block. This suggests an overlap between the dosage needed to produce adequate vasodilation for induced hypotension and the dosage that produces serious cardiac arrhythmia. Although the hemodynamic effects of diltiazem can be greatly modified by the various inhalational agents used during neurosurgery (see (11) for review), the polypharmacological effects of these drug combinations on ICP remains unknown.

In conclusion, although diltiazem's effect on ICP is minimal, its long duration of action and adverse cardiac effects (17–19) suggest that it is not a suitable agent for inducing controlled hypotension.

---

We thank Ms. Ellen L. Jackson for manuscript preparation, Dr. Bartol Matanic, DVM, for professional courtesies, and George McCoy for laboratory assistance.

## References

1. Cottrell JE, Gupta B, Turndorf H. Induced hypotension. In: Cottrell JE, Turndorf H, eds. Anesthesia and neurosurgery. St. Louis, MO: CV Mosby, 1980:387–400.
2. Siesko BK, Norberg K, Lyungpnen B, Salford LG. Hypoxia and cerebral metabolism. In: Gordon E, ed. A basis and practice of neuroanesthesia. Monographs in anesthesiology. New York: Excerpta Medica, 1975:47–82.
3. Edwinsson L, Brandt L, Andersson KE, et al. Effect of calcium antagonist on experimental constriction of human brain vessels. Surg Neurol 1979;11:327–30.
4. Murata S, Nagao T, Nakajima H. Cerebral vasodilation and spasmolytic activity of diltiazem in anesthetized animals. Japan J Pharmacol 1982;32:1033–40.
5. Giffin JP, Cottrell JE, Hartung J, Shwiry B. Intracranial pressure during nifedipine induced hypotension. Anesth Analg 1983;62:1078–80.
6. Bedford RF, Daley R, Win HR, Lynch C. Adverse impact of a calcium entry blocker (verapamil) on intracranial pressure in patients with brain tumor. J Neurosurg 1983;59:100–2.

7. Cottrell JE, Gupta B, Rappaport H, et al. Intracranial pressure during nitroglycerin induced hypotension. J Neurosurg 1980;53:309–11.
8. Taira N, Imai Y, Hiwatari M. Differential effects of nitroglycerin, trimetazidine, verapamil and SK & F 24260 on venous return as revealed by the open-loop method in the dog. Jpn J Pharmacol 1980;30:449–61.
9. Robinson BF, Dobbs RJ, Kelry CR. Effects of nifedipine on resistance vessels, arteries and veins in man. Br J Clin Pharmacol 1980;10:433–8.
10. Fleckenstein A. Specific pharmacology of calcium in myocardium, cardiac pacemakers, and vascular smooth muscle. Ann Rev Pharmacol Toxicol 1977;17:149–66.
11. Reves JG, Kissin I, Lell WA, et al. Calcium entry blockers: uses and implications for anesthesiologists. Anesthesiology 1982;57:504–18.
12. Polese A, Fiorentini C, Olivari MT, et al. Clinical use of a calcium antagonistic agent (nifedipine) in acute pulmonary edema. Am J Med 1979;66:825–30.
13. Kyuzo A, Tadashi Y, Setsuko K, et al. Hypotensive action and increased plasma renin activity by Ca$^2$ antagonist (nifedipine) in hypertensive patients. Japan Heart J 1976;17:479–84.
14. Pedersen OL, Mikkelsen E, Christensen NJ, et al. Effect of nifedipine on plasma renin, aldosterone and catecholamines in arterial hypertension. Eur J Clin Pharmacol 1979;15:235–40.
15. Singh BN, Roche AWG. Effects of intravenous verapamil on hemodynamics in patients with heart disease. Am Heart J 1977;94:593–9.
16. Matsumoto S, Ito T, Sada T, et al. Hemodynamic effects of nifedipine in congestive heart failure. Am J Cardiol 1980;46:476–80.
17. Kapur PA, Tippit SE. Correlation of cardiovascular effects with plasma levels of diltiazem during isoflurane anesthesia. Anesthesiology 1984;61:A12.
18. Kates RA, Zaggy AP, Norfleet EA, Heath KR. Comparative cardiovascular effects of verapamil, nifedipine, and diltiazem during halothane anesthesia in swine. Anesthesiology 1984;61:10–8.
19. Skarvan K, Priebe H, Gale J. Effects of diltiazem and isoflurane on cardiovascular function and coronary hemodynamics in dogs. Anesthesiology 1984;61:A9.

# Comparative Effects of Halothane, Enflurane, and Methoxyflurane on the Incidence of Abnormal Development Using Sea Urchin Gametes as an In Vitro Model System

Robert E. Hinkley, Jr, PhD, and Brent D. Wright, BS

HINKLEY RE JR, WRIGHT BD. Comparative effects of halothane, enflurane, and methoxyflurane on the incidence of abnormal development using sea urchin gametes as an in vitro model system. Anesth Analg 1985;64:1005–9.

*The incidence of sea urchin embryos developing abnormally after their exposure to equimolar concentrations of halothane, enflurane, and methoxyflurane has been determined. Halothane concentrations in the 0.6–1.25 mM range caused 18–96% of the embryos to undergo abnormal cleavage at the first cell division. This is important because embryos exhibiting atypical cleavage patterns at the first cell division eventually involute and die before reaching gastrulation. Over the same range of concentrations, enflurane and methoxyflurane have minimal effects on development. However, when exposed to 2.5 mM methoxyflurane, nearly 40% of the cells did not fertilize. These results show that volatile anesthetic agents have decidedly different effects on development and suggest that the incidence of abnormal development may not correlate directly with the anesthetic potency of inhalational agents.*

Key Words: ANESTHETICS, VOLATILE—halothane, enflurane, methoxyflurane. TOXICITY—teratogenicity.

Several reports have appeared in the literature describing the purported fetotoxic, "embryolethal," and teratogenic effects of volatile anesthetics in various animal model studies (1–4). These studies are, however, generally difficult to compare because of the use of different anesthetic agents and dosages, as well as the duration and timing of exposure. The inability to eliminate maternal stress as a possible cause of at least some of the effects observed has complicated these studies still further. Although some studies have failed to demonstrate an effect of volatile anesthetics on reproduction (5) or an appreciable effect on development (6,7), it has been concluded generally that "probably all inhalational anesthetics currently in use can cause embryotoxic effects when administered to pregnant animals at anesthetic concentrations for sufficient duration" (3).

As part of an ongoing research project aimed at defining the effects of inhalational anesthetic agents on early embryonic development, we compared the effects of halothane, enflurane, and methoxyflurane on fertilization and development through first cell division using sea urchin gametes as a model system. The purpose of these experiments was two-fold. First, we wanted to directly observe the effect of volatile anesthetics on the processes of fertilization and subsequent development using an in vitro model system. Second, we wanted to see whether any observed effects were related to the anesthetic potency of the agents tested.

## Materials and Methods

Sea urchins (*Lytechinus variegatus*) were collected locally and induced to spawn by routine methods described earlier (8). Eggs were washed in natural sea water (SW) containing 5 mM TAPS buffer (tris-hydroxymethyl-methylaminopropane sulfonic acid), pH 8.3. Sperm was collected in concentrated form in Syracuse dishes and placed on ice until used, usually within 1 hr.

Anesthetic solutions were prepared in 20-ml foil-lined screw-cap glass scintillation vials (8,9). A 10-μl gas-tight Hamilton syringe was used to add an amount of liquid anesthetic calculated to yield 0.3, 0.6, 1.25, or 2.5 mM in 20 ml of SW–TAPS. The anesthetic was dissolved by vigorous shaking of the vial.

For anesthetic exposure, 20-ml liquid scintillation

---

This study was supported by Research Grant GM 31723 from the Institute of General Medical Sciences, National Institutes of Health.

Received from the Departments of Anatomy and Cell Biology and Anesthesiology, The University of Miami School of Medicine, Miami, Florida. Accepted for publication May 7, 1985.

Address correspondence to Dr. Hinkley, Department of Anatomy and Cell Biology (R-124), The University of Miami School of Medicine, PO Box 016960, Miami, FL 33101.

© 1985 by the International Anesthesia Research Society

Table 1. Effect of Halothane, Enflurane, and Methoxyflurane on the Percentage of Dividing Sea Urchin Embryos Exhibiting Abnormal Cleavage Patterns at the First Cell Division

| Anesthetic | mM | *n* | % Abnormal | *P* |
|---|---|---|---|---|
| Halothane | 0.3 | 578 | 6.2 | <0.043 |
| | 0.6 | 544 | 17.6 | <0.0002 |
| | 1.25 | 569 | 96.1 | <<0.0001 |
| | 2.5 | 496 | 99.8 | <<0.0001 |
| | control | 534 | 3.6 | — |
| Enflurane | 0.3 | 333 | 4.5 | [a] |
| | 0.6 | 576 | 3.5 | [a] |
| | 1.25 | 578 | 3.8 | [a] |
| | 2.5 | 587 | 5.3 | <0.049 |
| | control | 685 | 3.1 | — |
| Methoxyflurane | 0.3 | 536 | 3.2 | [a] |
| | 0.6 | 489 | 4.3 | [a] |
| | 1.25 | 592 | 4.7 | [a] |
| | 2.5 | 398 | 36.7 | <<0.0001 |
| | control | 573 | 4.4 | — |

Abbreviation: *n*, total dividing cells counted.

[a] $P >> 0.5$. Control values do not differ significantly ($P >> 0.05$).

vials each were inoculated with 200,000 eggs. After the eggs settled to the bottom of the vial, the SW was aspirated and replaced with SW–TAPS containing known concentrations of halothane, enflurane, or methoxyflurane. Eggs were incubated with anesthetic for 15 min and then were fertilized (in the presence of anesthetic) by adding 200 μl of a stock sperm suspension (20 μl concentrated sperm in 20 ml SW–TAPS prepared just before use) to yield a final sperm/egg ratio of 2000:1. This ratio was used because recent work has shown that under these conditions fertilization is essentially complete and instantaneous with less than 5% polyspermy (10). Sperm and eggs were thoroughly mixed to ensure maximal interaction and allowed to settle for 5 min. The eggs were then resuspended in fresh SW–TAPS, transferred to Petri dishes, and allowed to develop through the first cell division, at which time the embryos were fixed in 5.6% formaldehyde in SW–TAPS, pH 8.0.

Embryos undergoing cytoplasmic division were scored as either dividing normally (symmetrical cleavage) or exhibiting abnormal (asymmetric) cleavage patterns. For counting purposes, abnormal cleavages were defined as those resulting in blastomeres of unequal number or size. The percentages of embryos dividing abnormally in experimental cultures were compared with those of control cultures by the two-tailed arcsine transformation method for testing the equality of percentages from unequal sample sizes (11). Differences were considered significant when $P < 0.05$. Necrotic cells as well as those remaining unfertilized at the time of the first cell division were also counted.

## Results

As can be seen in Table 1, halothane dose-dependently increased the incidence of cells exhibiting abnormal cleavage patterns at first division (compare Figure 1(*A*) with 1(*B*)–(*D*)). While the incidence of abnormally cleaving cells was only marginally affected by 0.3 mM halothane ($P < 0.05$), the incidence of abnormal cleavage increased significantly when eggs were fertilized in the presence of 0.6 mM halothane. When eggs were exposed to 1.25 mM halothane, the percentage of abnormally developing cells increased dramatically, to 96%; when eggs were exposed to 2.5 mM, nearly all dividing cells exhibited atypical cleavage patterns. At this concentration we also noted that 15% of all cells counted were necrotic by the first cell division (Table 2; Fig. 1(*E*)).

In contrast, enflurane had no appreciable effect on development over this same range of concentrations. Even when we used 2.5 mM enflurane, the highest concentration tested, the number of cells undergoing abnormal cleavage was only marginally larger than the abnormal controls ($P < 0.05$), and no increase in necrotic or unfertilized cells was observed (Table 2). Similarly, methoxyflurane concentrations of up to 1.25 mM also had no effect on development or on the percentage of cells appearing necrotic or remaining unfertilized. Concentrations of 2.5 mM methoxyflurane, however, provoked a marked increase in the number of embryos undergoing abnormal development, along with a slight increase in the number of necrotic cells (Table 2). In addition, exposure to 2.5 mM methoxyflurane caused a striking increase in the

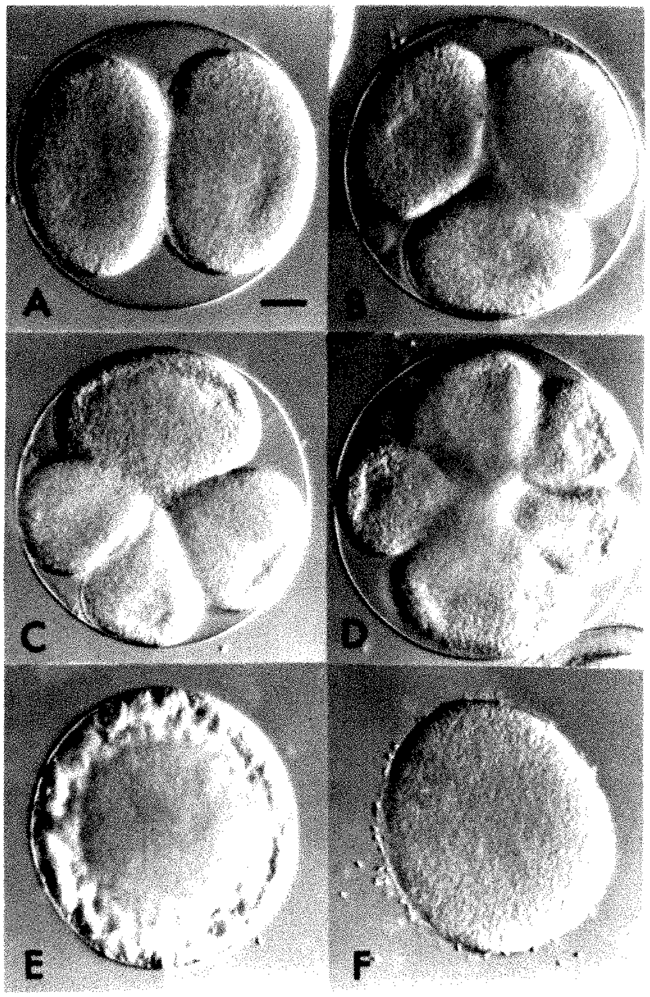


Figure 1. Nomarski differential interference contrast micrographs of sea urchin embryos fixed in 5.6% formaldehyde at the time of the first cell division. (*A*) Control cell undergoing the first cell division. Note symmetry of cleavage furrow and uniform size of blastomeres. Bar, 25 μm. (*B–D*) Halothane-treated cells fixed at the same time point as cell shown in *A*. Note supernumerary blastomeres resulting from multiple cleavage furrows. (*E*) Necrotic cell observed in halothane-treated culture. More than 15% of the cells became necrotic after exposure to 2.5 mM halothane. (*F*) Unfertilized cell in methoxyflurane-treated culture. Sperm bound to the egg surface are visible at the periphery. Nearly 40% of the eggs exposed to sperm in the presence of 2.5 mM methoxyflurane did not fertilize. All × 215.

number of cells remaining unfertilized (Table 2; Fig. 1(*F*)).

## Discussion

In this study we compared the developmental sensitivities of fertilized sea urchin eggs to equimolar concentrations of halothane, enflurane, and methoxyflurane. The results showed that development was most sensitive to halothane, relatively unaffected by enflurane, and modified by methoxyflurane only at a concentration of 2.5 mM. In this regard, it should be pointed out that the concentrations of anesthetics used in these experiments (and expressed in millimolarity) were chosen to span the range of concentrations used clinically and to correspond to concentrations in the gas phase (vol/vol) of 0.58–4.80% for halothane, 0.63–5.22% for enflurane, and 0.10–0.85% for methoxyflurane. These values were calculated assuming that the sea water/gas distribution coefficient at 25°C was similar to the saline/gas partition coefficients of these agents. The saline/gas partition coefficients used in these calculations were taken to be equal to 0.95 (12) that of the water/gas partition coefficient (13). The assumed sea water/gas coefficients were 1.2 for halothane, 1.1 for enflurane, and 7.0 for methoxyflurane.

These data show that volatile anesthetics clearly differ in their ability to promote abnormal development in the in vitro sea urchin model system. The ability of the agents tested to modify development does not appear to correlate directly with their relative anesthetic potencies (MAC) in humans (14). If the incidence of abnormal development were related to anesthetic potency, then we should have observed numbers of abnormally developing embryos in proportion to the relative potencies of the anesthetics examined. Based on human MAC values (about 0.2% for methoxyflurane, 0.8% for halothane, and 1.7% for enflurane (14)), the relative anesthetic potency of methoxyflurane is approximately four times greater than halothane and eight times greater than enflurane. The data in Table 1, however, show that these anticipated ratios were not obtained over the range of concentrations tested. The lack of proportionality is most easily seen by comparing the percentages of abnormally developing embryos after exposure to 0.3 mM methoxyflurane, 1.25 mM halothane, and 2.5 mM enflurane. At these concentrations we would have expected to encounter roughly equal numbers of abnormally dividing cells if abnormal development were related to anesthetic potency. Although 0.3 mM methoxyflurane and 2.5 mM enflurane have no detectable and only marginal effects, respectively, halothane induced more than 96% of the embryos to undergo abnormal development. Thus we conclude that the incidences of abnormal development induced by these inhalational agents do not correlate with their anesthetic potencies.

The possibility that thymol, added as a preservative to halothane, might be responsible for these effects was discounted when we compared the data shown for halothane in Table 1 with data from experiments in which halothane was distilled to remove thymol. We could detect no statistically significant difference in the incidences of abnormal development whether

Table 2. Effect of Halothane, Enflurane, and Methoxyflurane on the Percentage of Cells Appearing Necrotic or Remaining Unfertilized at the First Cell Division

| Anesthetic | mM | *n* | % Necrotic | *P* | % Unfertilized | *P* |
|---|---|---|---|---|---|---|
| Halothane | 0.3 | 589 | 1.9 | [a] | 0 | [a] |
| | 0.6 | 552 | 1.4 | [a] | 0 | [a] |
| | 1.25 | 592 | 3.7 | <0.0001 | 0.2 | [a] |
| | 2.5 | 586 | 15.3 | <<0.0001 | 0 | [a] |
| | control | 538 | 0.6 | | 0.2 | — |
| Enflurane | 0.3 | 336 | 0.9 | [a] | 0 | [a] |
| | 0.6 | 579 | 0.6 | [a] | 0 | [a] |
| | 1.25 | 584 | 0.9 | [a] | 0.2 | [a] |
| | 2.5 | 594 | 1.2 | [a] | 0 | [a] |
| | control | 694 | 0.9 | | 0.1 | — |
| Methoxyflurane | 0.3 | 538 | 0.2 | [a] | 0.2 | [a] |
| | 0.6 | 491 | 0.4 | [a] | 0 | [a] |
| | 1.25 | 595 | 0.6 | [a] | 0 | [a] |
| | 2.5 | 658 | 1.5 | <0.008 | 38.0 | <<0.0001 |
| | control | 575 | 0.2 | | 0.2 | — |

Abbreviation: *n*, total cells counted.

[a] $P >> 0.05$. Controls do not differ significantly ($P >> 0.05$).

thymol was present or absent. Accordingly, thymol does not appear to be responsible for the abnormal development seen in experiments with halothane.

These studies confirm and extend our previous work (8) showing that halothane can alter development when exposure is started at metaphase or before. In this study we have shown that abnormal development at the first cell division can be induced by exposure to halothane at the time of fertilization. Microscopic examinations of unfixed embryos undergoing abnormal development in response to halothane exposure revealed the presence of supernumerary sperm asters. This observation strongly suggests that the abnormal development subsequently seen when eggs are fertilized in the presence of halothane is due to polyspermy. In fact, preliminary studies with halothane-treated eggs show that the incidence of polyspermy correlates exactly with the number of embryos that subsequently undergo abnormal cleavage. These observations suggest that halothane, and perhaps elevated concentrations of methoxyflurane as well, may in some way alter the egg membrane to impair the electrical block to multiple sperm entry at fertilization (see reference (15) for a review of the membrane potential changes accompanying fertilization in the sea urchin). Experiments are in progress to test this hypothesis by examining the effects of halothane on egg membrane potentials before and during fertilization.

The high incidence of cells that did not become fertilized complicates our analysis of the data for methoxyflurane. Although difficult to attribute to a specific effect, we believe that the failure of fertilization in this case may be due to a "spermicidal" effect of high levels of methoxyflurane, or at least to a dramatic reduction in sperm motility. Related to this supposition, halothane has been shown to inhibit sperm motility dose-dependently and reversibly (9). Whether methoxyflurane has a similar effect on sperm motility (which could severely lessen the number of effective sperm–egg collisions) or acts by altering the egg plasma membrane to prevent fertilization, remains to be determined. The possibility that methoxyflurane prevents fertilization by inhibiting sperm–egg binding can be ruled out because sperm bound to the surface of unfertilized eggs are plainly visible (Fig. 1(*F*)).

Although we caution against extrapolating these data to mammalian systems, our data clearly show that volatile anesthetics can alter early development in vitro. Furthermore, our data raise the possibility that polyspermy may be, at least in part, responsible for the increase in mammalian fetal resorptions observed during halothane exposure (1,3,4). Wharton et al. (3) have attributed lowered pregnancy rates and decreased numbers of implantations to a variety of factors including production of nonviable ova, failure of fertilization or implantation, or very early postimplantation wastage. Our halothane experiments suggest that an effect may occur at the level of the egg plasma membrane that modifies the process of fertilization to promote polyspermy. We feel that the production of nonviable ova as a cause of the decreased fertility noted by Wharton et al. (1) is unlikely because the effects on development reported here are completely reversible if halothane is removed before fertilization. In general, we agree with the conclusion of Wharton et al. (3) that probably all inhalational anesthetics can affect development when administered in sufficient concentration. However, our results show that development may be modified by anesthetics through direct action on the embryo (or gametes) and raise the possibility that the molecular mechanisms by which various anesthetics ultimately affect fertilization and development may be different.

Our conclusion that there appears to be no direct correlation between the relative potency of inhalational anesthetics and their ability to alter embryogenesis may also apply to narcotic analgesics as well. In a recent report, Bruce et al. (16) showed that fentanyl had no detectable effect on fertilization or development of sea urchin eggs even at concentrations far exceeding those used clinically. In contrast, Cardasis and Schuel (17) found significant increases in the percentages of abnormally developing echinoderm embryos after fertilization in the presence of clinically relevant doses of morphine. These previous observations, along with the results of our present study, indicate that it is impossible to predict, based solely on relative clinical potency, the extent to which either inhalational anesthetics or narcotic analgesics will adversely affect embryogenesis.

We wish to thank Drs. David Bruce, Edward Chambers, and Harry Linde for reviewing the manuscript.

## References

1. Wharton RS, Mazze RI, Badden JM, Hitt BA, Dooley JR. Fertility, reproduction and postnatal survival in mice chronically exposed to halothane. Anesthesiology 1978;48:167–74.
2. Lane GA, Nahrwold ML, Tait AR, Taylor-Busch M, Cohen PJ, Beaudoin AR. Anesthetics as teratogens: nitrous oxide is fetotoxic, xenon is not. Science 1980;210:899–901.
3. Wharton RS, Sievenpiper TS, Mazze RI. Developmental toxicity of methoxyflurane in mice. Anesth Analg 1980;59:421–5.
4. Bussard DA, Stoelting RK, Peterson C, Ishaq M. Fetal changes in hamsters anesthetized with nitrous oxide and halothane. Anesthesiology 1974;41:275–8.
5. Bruce DL. Murine fertility unaffected by traces of halothane. Anesthesiology 1973;38:473–7.
6. Lansdown ABG, Pope WDB, Halsey MJ, Bateman PE. Analysis of fetal development in rats following maternal exposure to subanesthetic concentrations of halothane. Teratology 1976; 13:299–304.
7. Pope WDB, Halsey MJ, Lansdown ABG, Simmonds A, Bateman PE. Fetotoxicity in rats following chronic exposure to halothane, nitrous oxide, or methoxyflurane. Anesthesiology 1978; 48:11–6.
8. Hinkley RE, Chambers EL. Structural changes in dividing sea-urchin eggs induced by the volatile anesthetic halothane. J Cell Sci 1982;55:327–39.
9. Hinkley RE. Inhibition of sperm motility by the volatile anesthetic halothane. Exp Cell Res 1979;121:435–9.
10. Hinkley RE, Wright BD. Isolation of intact sperm asters from fertilized sea urchin eggs. J Exp Zool 1985;233:473–7.
11. Sokal RR, Rohlf FJ. Biometry: the principles and practice of statistics in biological research. San Francisco, CA: W.H. Freeman, 1969:608.
12. Renzi F, Waud BE. Partition coefficients of volatile anesthetics in Krebs' solution. Anesthesiology 1977;47:62–3.
13. Halsey MJ. Physicochemical properties of inhalational anesthetics. In: Gray TC, Nunn JF, Utting JE, eds. General Anesthesia, 4th ed. Boston, MA: Butterworth, 1980:53.
14. Eger EI. Anesthetic uptake and action. Baltimore, MD: Williams and Wilkins Company, 1974:5.
15. Nuccitelli R, Grey RD. Controversy over the fast, partial, temporary block to polyspermy in sea urchins: a reevaluation. Dev Biol 1984;103:1–17.
16. Bruce DL, Hinkley R, Norman PF. Fentanyl does not inhibit fertilization or early development of sea urchin eggs. Anesth Analg 1985;64:498–500.
17. Cardasis C, Schuel H. The sea urchin egg as a model system to study effects of narcotics on secretion. In: Ford DH, Clouet DH, eds. Tissue responses to additive drugs. New York, NY: Spectrum, 1976:631–40.

1010 ANESTH ANALG
1985;64:1010–4

## Clinical Reports

# Atracurium Pretreatment for Succinylcholine-induced Fasciculations and Postoperative Myalgia

Laxmaiah Manchikanti, MD, J. Blane Grow, MD, Jerry A. Colliver, PhD,
Michael G. Canella, BS, CRNA, and Clyde H. Hadley, BS, CRNA

Pretreatment with a nondepolarizing muscle relaxant is commonly accepted as standard clinical practice for the alleviation of fasciculations, myalgia, and other undesirable sequelae associated with succinylcholine administration (1–11). Atracurium besylate, a new nondepolarizing muscle relaxant with numerous desirable properties (12), has not been evaluated for prophylaxis against the undesirable sequelae associated with succinylcholine administration. Hence, this prospective study was undertaken to evaluate the efficacy of atracurium pretreatment, 0.05 mg/kg, on neuromuscular blockade and prevention of fasciculations and myalgia produced by succinylcholine administration, 1.0 mg/kg and 1.5 mg/kg.

## Materials and Methods

Eighty outpatients without known contraindications to succinylcholine undergoing elective arthroscopy under general anesthesia were randomly allocated into four groups with 20 patients in each group. This study was approved by the Institutional Review committee, and informed consent was obtained from all the patients. All patients received ranitidine, 150 mg, and metoclopramide, 10 mg, orally, as well as meperidine, 50 mg, and prochlorperazine, 5 mg intravenously, 45–120 min before induction of anesthesia. Pretreatment was administered in a double-blind fashion and consisted either of normal saline or atracurium, which were labeled as solutions *A* or *B*. Atracurium was diluted to 0.5 mg/ml. Syringes were prepared and labeled by an investigator who also allocated the patients into four groups but did not participate in evaluation of fasciculations, mylagia, or further follow-up. The code was broken only after completion of the study. Atracurium dosage for pretreatment, 0.05 mg/kg, was selected, as this represents 25% of $ED_{95}$ and 10% of the dosage required to completely depress muscle twitch tension, and 0.06 mg/kg was shown to result in neuromuscular blockade less than 5% (12).

Patients in groups I and II served as controls and received normal saline for pretreatment followed by succinylcholine, 1.0 mg/kg (group I) or 1.5 mg/kg (group II). Patients in groups III and IV received atracurium pretreatment, 0.05 mg/kg, prior to succinylcholine administration, either 1.0 mg/kg (group III) or 1.5 mg/kg (group IV). Normal saline or atracurium, 0.1 ml/kg, was administered 3–5 min before succinylcholine. Anesthesia was induced with thiopental, 4–5 mg/kg. Succinylcholine was administered after loss of lid reflex. Maintenance of anesthesia was carried with isoflurane and nitrous oxide.

The intensity of fasciculations and the onset and duration of the neuromuscular blockade was evaluated visually. The intensity of fasciculations in face, neck, shoulders, trunk, and upper and lower extremity musculature was scored from 0 to 3 (0, no fasciculations; 1, just visible fibrillations; 2, moderate contractions; 3, vigorous contractions). Onset and duration of the neuromuscular blockade were evaluated by observing 1-sec twitch response to supramaximal stimulation of the ulnar nerve via subcutaneous electrodes. The duration in seconds from the injection of succinylcholine to maximum suppression of twitch, abolition of twitch, reappearance of twitch, and full recovery of twitch was recorded. Time to maximum suppression of twitch differed from time to abolition

---

Received from the Department of Anesthesiology, Lourdes Hospital, Paducah, Kentucky, and the Department of Statistics and Measurement, Southern Illinois University School of Medicine, Springfield, Illinois. Accepted for publication April 16, 1985.

Address correspondence to Dr. Manchikanti, Department of Anesthesiology, Lourdes Hospital, 1530 Lone Oak Road, Paducah, KY 42001.

© 1985 by the International Anesthesia Research Society

Table 1. Patient Characteristics

| | Number of patients | Age in yr (mean ± SEM) | Height in cm (mean ± SEM) | Weight in kg (mean ± SEM) | Pretreatment interval in min (mean ± SEM) |
|---|---|---|---|---|---|
| Group I<br>Normal saline plus<br>1.0 mg/kg succinylcholine | 20 | 30.0 ± 2.7 | 173 ± 2.2 | 73.5 ± 3.9 | 3.65 ± 0.13 |
| Group II<br>Normal saline plus<br>1.5 mg/kg succinylcholine | 20 | 38.3 ± 3.2 | 177 ± 1.8 | 83.7 ± 2.5 | 3.55 ± 0.15 |
| Group III<br>0.05 mg/kg Atracurium plus<br>1.0 mg/kg succinylcholine | 20 | 39.6 ± 2.7 | 178 ± 1.5 | 82.4 ± 3.1 | 3.50 ± 0.15 |
| Group IV<br>0.05 mg/kg Atracurium plus<br>1.5 mg/kg succinylcholine | 20 | 36.3 ± 4.1 | 174 ± 1.9 | 75.2 ± 3.4 | 3.65 ± 0.17 |
| Direction and significance of values[a] | | I = II = III = IV | I = II = III = IV | I = II = III = IV | I = II = III = IV |

[a] No significant differences.

of twitch with continued presence of flicker of contraction. In most cases these response times were different. In some cases both these responses were achieved at the same time, while in a few cases abolition of twitch was not observed.

Postoperative muscle pains were evaluated and recorded by postoperative telephone interviews conducted by one of the authors who was unaware of group assignment and fasciculations. Each patient was interviewed on the first and second postoperative days. The interviewer asked a series of standard questions followed by specific questions: "Do you have, or have you had any pain or stiffness in your muscles following your operation other than the knee wherein the arthroscopy was performed?" If the answer was yes, the location, duration, severity of pain, and necessity for pain medication were recorded. Postoperative interviews were continued on a daily basis until postoperative muscle pains were resolved. Myalgia was graded according to its severity from 0 to 3 (0, no pain, absence of complaints either spontaneously or on direct questioning; 1, mild pain, limited to one area of the body, mild in nature, usually elicited on direct questioning but not requiring analgesics; 2, moderate pains, involving more than one area of the body, moderately severe in nature; 3, severe pains, generalized, severe in nature, often incapacitating and requiring analgesics).

Statistical analyses were performed by analyses of variance (ANOVAs) and $\chi^2$ analyses. One-way ANOVAs with Duncan's multiple-range follow-up tests were used to test the significance of differences among the means of the four groups. Two-way (2 × 2) ANOVAs were used to test the effects of atracurium and succinylcholine dosage. Overall and follow-up $\chi^2$ analysis were performed to compare proportions of patients in the four groups assigned to graded categories representing intensity of fasciculations and severity of body pain. Results were considered statistically significant if $P$ values were less than 0.05.

## Results

Demographic information for patients in the four groups is summarized in Table 1. Sex distribution, age, height, weight, and pretreatment interval did not differ significantly among the four groups.

### *Neuromuscular Blockade*

The groups differed significantly in terms of the mean time from succinylcholine administration to maximum suppression of twitch response, ($P = 0.0080$, Table 2). The mean time interval for maximum suppression of twitch was significantly longer for the two groups receiving atracurium (groups III and IV) than for the control groups (groups I and II, $P < 0.05$). There were no significant differences among the four groups in terms of mean time interval from succinylcholine administration to abolition of twitch. However, the pooled mean duration (84.1 sec) of the two atracurium-pretreated groups (groups III and IV) was significantly greater than the pooled mean duration (61.9 sec) of the two control groups (groups I and II, $P = 0.0082$).

There were significant differences among the four groups in terms of mean time from succinylcholine administration to return of twitch ($P = 0.0001$). This duration was significantly longer in group II (control with succinylcholine, 1.5 mg/kg) than in the other

Table 2. Twitch Responses to Electrical Stimulation

| | Onset of neuromuscular blockade | | Duration of neuromuscular blockade | |
|---|---|---|---|---|
| | Maximum suppression of twitch response in sec (mean ± SEM) | Abolition of twitch response in sec (mean ± SEM) | Return of twitch response in sec (mean ± SEM) | Full recovery of twitch response in sec (mean ± SEM) |
| Group I | 53.3 ± 3.8 | 60.1 ± 3.8 | 442 ± 41.9 | 516 ± 35.7 |
| Group II | 52.4 ± 3.1 | 63.6 ± 3.1 | 660 ± 43.0 | 808 ± 50.1 |
| Group I plus group II | 52.8 ± 2.4 | 61.9 ± 2.4 | 554 ± 34.5 | 662 ± 38.3 |
| Group III | 74.6 ± 5.4 | 82.8 ± 7.2 | 314 ± 29.6 | 445 ± 21.8 |
| Group IV | 69.9 ± 8.3 | 85.3 ± 13.5 | 381 ± 31.7 | 486 ± 32.7 |
| Group III plus group IV | 72.2 ± 4.9 | 84.1 ± 7.9 | 350 ± 22.3 | 465 ± 19.7 |
| Direction and significance of values | III = IV > I = II | I = II = III = IV | II > I, III, IV<br>I > III and I = IV | II > I = III = IV |

three groups (groups I, III, and IV) and was significantly greater in group I (control with succinylcholine, 1.0 mg/kg) than in group III (atracurium with succinylcholine, 1.0 mg/kg), $P < 0.05$). However, the difference between groups I and IV was not statistically significant. The pooled mean duration (554 sec) of the two control groups (groups I and II) to return of twitch was significantly greater than the pooled mean duration (350 sec) of the two atracurium-pretreated groups (groups III and IV, $P = 0.0004$). The four groups also differed significantly in terms of mean duration from succinylcholine administration to full recovery of twitch ($P = 0.0001$). Full recovery time was significantly greater in group II than in groups I, III, and IV ($P < 0.05$), but the latter three groups did not differ significantly. However, the pooled mean duration (662 sec) of the two control groups (groups I and II) was significantly greater than the pooled mean duration (465 sec) of the two atracurium-pretreated groups (groups III and IV, $P = 0.0001$).

### *Fasciculations*

There were significant differences among the four groups with respect to mean fasciculation intensity ($P = 0.0003$, Table 3). The two groups receiving atracurium pretreatment (groups III and IV) had significantly lower mean fasciculation intensity than the two control groups (groups I and II, $P < 0.05$). There were no significant differences between either groups I and II or groups III and IV.

The four groups also differed significantly in terms of proportion of patients with fasciculations ($P = 0.0003$). The two atracurium-pretreated groups (groups III and IV) had significantly fewer patients with fasciculations than the two control groups (groups I and II, $P < 0.05$). Groups I and II did not differ significantly, and groups III and IV did not differ significantly.

### *Muscle Pains*

There were significant differences among the four groups with respect to mean severity of postoperative graded muscle pain ($P = 0.0033$, Table 4). Two groups receiving atracurium (groups III and IV) had mean muscle pain significantly less severe than the two control groups (groups I and II, $P < 0.05$). Groups I and II and groups III and IV did not differ significantly.

The four groups also differed significantly in terms of the proportion of patients with body pains ($P = 0.0077$). The two atracurium-pretreated groups (groups III and IV) had significantly fewer patients with body pains than the two control groups (groups I and II, $P < 0.05$). Groups I and II and groups III and IV did not differ significantly.

### *Correlation of Fasciculations and Myalgia*

The preceding shows a "between groups" relationship between fasciculations and myalgia, in that the two atracurium-pretreated groups were lower with respect to incidence and severity of fasciculations and incidence and severity of postoperative myalgia than the two control groups. This direct relationship of fasciculation and myalgia found between groups, however, was not obtained "within groups." The correlation coefficients computed between fasciculations and myalgia for each of the four groups separately ranged from −0.05 to +0.39, and none were statistically significant. The correlation coefficient computed between fasciculations and myalgia for the four groups combined, adjusted for the respective group

Table 3. Characteristics of Fasciculations

| | Graded intensity of fasciculations (mean ± SEM) | Patients with fasciculations | Patients with no fasciculations | Patients with visible fibrillations | Patients with moderate contractions | Patients with vigorous contractions |
|---|---|---|---|---|---|---|
| Group I | 1.80 ± 0.22 | 18<br>(90%) | 2<br>(10%) | 6<br>(30%) | 6<br>(30%) | 6<br>(30%) |
| Group II | 1.90 ± 0.27 | 17<br>(85%) | 3<br>(15%) | 6<br>(30%) | 1<br>( 5%) | 10<br>(50%) |
| Group III | 0.85 ± 0.22 | 10<br>(50%) | 10<br>(50%) | 4<br>(20%) | 5<br>(25%) | 1<br>( 5%) |
| Group IV | 0.65 ± 0.23 | 7<br>(35%) | 13<br>(65%) | 3<br>(15%) | 2<br>(10%) | 2<br>(10%) |
| Direction and significance of values | I = II > III = IV | I = II > III = IV | I = II < III = IV | | | |

means and standard deviations, was +0.09, also not significant.

## Discussion

The incidence of postoperative myalgia following succinylcholine has been reported as 0.2–89% (1–11). This high variability is attributed to factors such as age, sex, type of premedication, type of operation, type of anesthetic, and time to postoperative ambulation. Hence, the comparison of these reports, either with each other or with the present study, is difficult. However, many investigators think that postoperative muscle pains occur more frequently in females, in ambulatory patients, and in patients who have undergone minor surgical procedures. This study focused on patients, all of whom underwent the same surgical procedure and received the same premedication and anesthetic, and all of whom ambulated at a similar time postoperatively, namely 2–4 hours. Patients were also similar in all groups with respect to sex, height, and weight.

Similarly to previous reports, in this study fasciculations were observed in 85 and 90% and muscle pains in 45 and 50% of the control patients receiving either 1.0 mg/kg or 1.5 mg/kg succinylcholine. Pretreatment with atracurium, 0.05 mg/kg, 3–5 minutes before administration of succinylcholine, 1.0 mg/kg or 1.5 mg/kg, markedly reduced the frequency and intensity of fasciculations. Fasciculations were seen in 35 and 50% of patients, and muscle pains were seen in only 10 and 15% of the patients with atracurium pretreatment. There were no differences between the two control groups receiving succinylcholine, either 1.0 mg/kg or 1.5 mg/kg, with respect to incidence of either frequency and intensity of fasciculations or postoperative myalgia. There were also no differences between the two control groups with respect to onset of neuromuscular blockade, though duration of neuromuscular blockade was significantly longer with 1.5 mg/kg of succinylcholine than with 1.0 mg/kg. With respect to the effect of atracurium pretreatment, there were no disadvantages noted by increasing succinylcholine dosage by 50% (1.5 mg/kg vs 1.0 mg/kg) in regard to frequency and intensity of fasciculations and muscle pains. However, atracurium pretreatment delayed onset of neuromuscular blockade in both atracurium groups and shortened the recovery time. There were three patients in groups III and IV in whom abolition of twitch was not achieved. Succinylcholine, 1.5 mg/kg, after atracurium pretreatment maintained neuromuscular blockade for a longer period than succinylcholine, 1.0 mg/kg, which was equivalent to the blockade achieved by 1.0 mg/kg of succinylcholine without pretreatment.

The mechanism of succinylcholine-induced myalgia is not clear. Irreversible changes in muscle spindles, unsynchronized contraction of muscle fibers resulting in a shearing force on connective tissue, and electrolyte imbalance are among the various explanations posed for postoperative muscle pains (13–15). Correlation between succinylcholine-induced fasciculations and body pain has been suggested by some investigators. Hence, various ways of diminishing muscle fasciculations have been studied, nondepolarizing muscle relaxants being most commonly utilized for this purpose. Although we found a between groups relationship between fasiciculations and myalgia, in that patients receiving atracurium had fewer fasciculations and less myalgia than controls, fasciculations and myalgia were not related within groups. The majority of patients (75%) with postoperative myalgia also had fasciculations.

The results in this study are consistent with previous studies. In comparison with previous studies, the effects of atracurium for attenuation of frequency

Table 4. Distribution of Patients with Postoperative Myalgia

| | Graded intensity of muscle pains (mean ± SEM) | Patients with muscle pains | Patients with no pains | Patients with mild pains | Patients with moderate pains | Patients with severe pains |
|---|---|---|---|---|---|---|
| Group I | 1.05 ± 0.28 | 10<br>(50%) | 10<br>(50%) | 3<br>(15%) | 3<br>(15%) | 4<br>(20%) |
| Group II | 1.00 ± 0.27 | 9<br>(45%) | 11<br>(55%) | 1<br>( 5%) | 5<br>(25%) | 3<br>(15%) |
| Group III | 0.30 ± 0.18 | 3<br>(15%) | 17<br>(85%) | 1<br>( 5%) | 1<br>( 5%) | 1<br>( 5%) |
| Group IV | 0.10 ± 0.07 | 2<br>(10%) | 18<br>(90%) | 2<br>(10%) | 0<br>( 0%) | 0<br>( 0%) |
| Direction and significance of values | I = II > III = IV | I = II > III = IV | I = II < III = IV | | | |

and severity of postoperative myalgia with atracurium observed in the present study are comparable to the results of studies in which other nondepolarizing muscle relaxants were used. It will be interesting to see the effect of a higher dose of atracurium pretreatment on fasciculations and muscle pains. However, with increase in atracurium pretreatment dosage, we expect further delay in the onset and reduction in the intensity of neuromuscular blockade that will necessitate further increase of succinylcholine dosage.

In summary, succinylcholine-induced fasciculations and postoperative myalgia were attenuated to a significant extent by prior administration of atracurium. Atracurium pretreatment also delayed the onset and reduced the intensity of neuromuscular blockade. Increasing succinylcholine dosage by 50% (1.0 mg/kg vs 1.5 mg/kg) increased the duration of neuromuscular blockade equivalent to neuromuscular blockade achieved with 1.0 mg/kg of succinylcholine without pretreatment. We conclude that atracurium pretreatment is an effective technique for attenuation of succinylcholine-induced fasciculations and myalgia.

Our special thanks to Drs. Hunt, Morehead, Thomas, and Wilkinson (orthopedic surgeons) and John Germain, Surgery Supervisor, for their help in completion of this study. We are also grateful to Anesthesia and Operating Room staff and Mike Ferguson for their cooperation and help.

## References

1. Durant NN, Katz RL. Suxamethonium. Br J Anaesth 1982;54:195–208.
2. Churchill-Davidson HC. Suxamethonium chloride and muscle pains. Br Med J 1957;1:383–4.
3. Cullen DJ. The effect of pretreatment with non-depolarizing muscle relaxant on neuromuscular blocking action of succinylcholine. Anesthesiology 1971;35:572–8.
4. Brodsky JB, Brock-Utne JG, Samuels SI. Pancuronium pretreatment and postsuccinylcholine myalgias. Anesthesiology 1979;51:259–61.
5. Blitt CD, Carlson GL, Rolling GD, Hammeroff SR, Otto CW. A comparable evaluation of pretreatment with non-depolarizing neuromuscular blockers prior to the administration of succinylcholine. Anesthesiology 1981;55:687–9.
6. Ferres CJ, Mirakhur RK, Craig HJL, Browne ES, Clarke RSJ. Pretreatment with vecuronium as a prophylactic against post-suxamethonium muscle pain. Br J Anaesth 1983;55:735–40.
7. Baraka A. Self-taming of succinylcholine induced fasciculations. Anesthesiology 1977;46:292–3.
8. Wilson DB, Dundee JN. Failure of divided doses of succinylcholine to reduce the incidence of muscle pains. Anesthesiology 1980;52:272–5.
9. Fahmy NR, Malek NS, Lappas GD. Diazepam prevents some adverse effects of succinylcholine. Clin Pharmacol Ther 1979;26:395–8.
10. Manchikanti L. Diazepam does not prevent succinylcholine-induced fasciculations and myalgia. A comparative evaluation of the effect of diazepam and *d*-tubocurarine pretreatments. ACTA Anaesthesiol Scand 1984;28:523–8.
11. Haldia KN, Chatterji S, Kackar SN. Intravenous lignocaine for prevention of muscle pain after succinylcholine. Anesth Analg 1973;52:849–52.
12. Basta SJ, Ali HH, Saverese JJ, et al. Clinical pharmacology of atracurium besylate (BW 33A): a new non-depolarizing muscle relaxant. Anesth Analg 1982;61:723–9.
13. Rack PMH, Westbury DR. The effects of suxamethonium and acetylcholine on the behavior of cat muscle spindles during dynamic stretching and during fusimotor stimulation. J Physiol (London) 1966;186:698–706.
14. Waters DJ, Mapleson WW. Suxamethonium pains—hypothesis and observation. Anaesthesia 1971;26:127–41.
15. Collier CB. Suxamethonium pains and early electrolyte changes. Anaesthesia 1978;33:454–61.

ANESTH ANALG
1985;64:1015–6

# Inflation Device to Prevent Aortocaval Compression during Pregnancy

Gerhard C. Endler, MD, and Rolf W. Donath, MD

Aortocaval compression by the uterus is well recognized as a complication of late pregnancy in a woman who assumes the supine position. It may cause maternal hypotension and decreased uteroplacental blood flow. The condition is alleviated by lateral displacement of the uterus, or by turning the patient on her side. We describe a simple inflatable device that, when properly placed under the mattress of the operating table, raises the parturient's right hip and thereby produces a 15° tilt of the pelvis.

## Methods

The inflation device, depicted in Figure 1, consists of a 1000-ml pressure administration cuff (*A*) of the type commonly used to administer blood under pressure (Sorenson Research, Salt Lake City, UT) and a source of compressed gas to inflate the cuff. The two nipples issuing from the cuff are bared of their attachments (aneroid manometer and inflation bulb). The manometer (*B*) is reattached to one nipple by means of a 100-cm-long piece of Baumanometer straight latex tubing (W. A. Baum Co., Piague, NY), and similar tubing, 250-cm long (*C*), is attached to the other. Before its use, the administration cuff is encased in a pillow cover and placed under the mattress in such a way that the distal end of the cuff lies under the greater trochanter of the parturient. Both tubes are tucked under the mattress and so arranged that they emerge at the head of the table. The manometer allows the cuff pressure to be monitored while the second tubing is connected to one of two systems that may be used to power the unit.

The first system (system 1) is very simple and operates independently of any other power source. It consists of the pressure regulator portion of a Pneumatic Tourniquet (Walter Kidde and Company, Bloomfield, NJ) whose circular inflatable cuff has been removed (*D*). It is connected to the pressure administration cuff by means of tubing (*C*). The regulator incorporates a Medic-Air Refill bottle that generates gas for inflation. After adjusting the inflation pressure to 300 mm Hg, the device is turned on, and the cuff fills in 12 sec to a width of 10.5 cm.

The second system (system 2) is considerably less expensive and essentially free of maintenance. It is, however, not as easy to assemble and requires an external power source. The central element of the system is a Conoflow H10 XTH 103 kPa gauge pressure range Manual Loading Regulator (Control Equipment Co., Salt Lake City, UT). Interposed between the wall outlet for air (or oxygen, if air is unavailable) and the administration cuff, it reduces gas pressure to a preset value of 300 mm Hg. To allow activation and deactivation of the system, a Puritan Quick Connect System (Puritan–Bennett Co., Kansas City, MO) is attached to the low pressure port of the regulator. The entire system is arranged in the following sequence: pressure administration cuff (*A*); tubing (*C*), quick connect adapter, hose crimp to quick connect adapter (*E*), quick connect valve, 6.35-mm 18 NPT male thread with service valve (*G*), regulator (*H*), adapter 6.35-mm NPT male thread to 6.35-mm inner diameter barbed hose nipple adapter (*I*), crimp-on ferrule (*J*), high pressure hose (*K*), and gas outlet (*L*). Ideally, one wall outlet (air or oxygen) should be dedicated to the system because the administration cuff deflates when the pressure hose is disconnected from the outlet. If no separate outlet is available, a double outlet adapter can be used to both power the device and supply air or oxygen to the anesthesia machine. The system is activated, and the cuff inflates in 6 sec when connection is made at location *F* in the system, while disconnection causes the cuff to slowly empty. The Quick Connect System (*E*,*G*) operates on a similar principle as the quick connect gas-hose connector of the anesthetic supply system.

---

Received from the Departments of Anesthesiology, Wayne State University, Hutzel Hospital, and Detroit Receiving Hospital, Detroit, Michigan. Accepted for publication April 22, 1985.

Address correspondence to Dr. Endler, Department of Anesthesiology, Hutzel Hospital, 4707 St. Antoine Blvd., Detroit, MI 48201.

© 1985 by the International Anesthesia Research Society

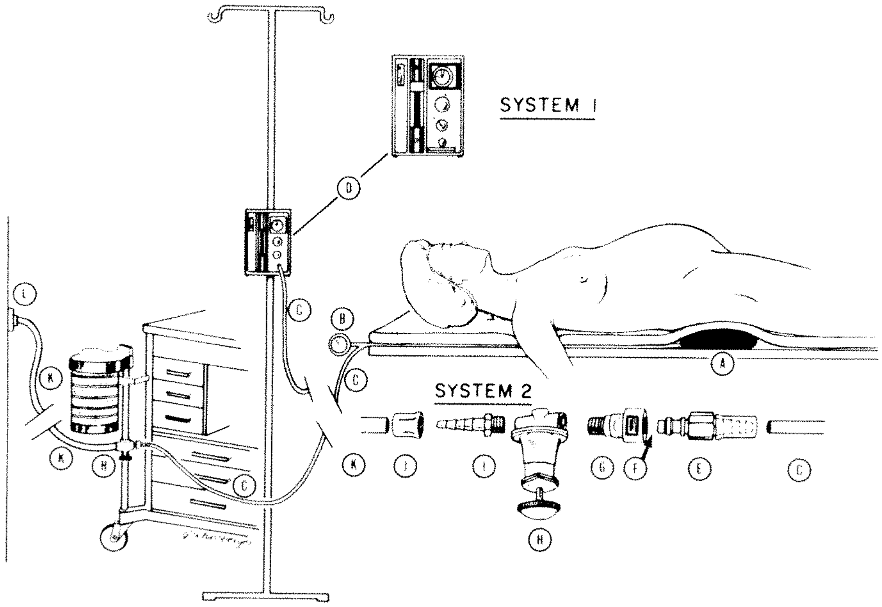


Figure 1. Inflation device powered either by a pressure regulator with built-in gas supply, or by compressed gas from central gas supply system with in-line regulator. For details see text.

## Discussion

Elevation of the right hip can be achieved in a number of ways (folded sheet, wedge-shaped piece of foam rubber), but the use of an inflatable device that can be remotely inflated and deflated appears most practical. The simplest such device consists of a discarded 3-L plastic bag containing urologic irrigating fluid and a sphygmomanometer inflating bulb with attached control valve (1). Both are connected by tubing of appropriate length, and the bag is manually inflated when the need arises. After using the device for some time, we have found that manual inflation is time-consuming and, particularly following the administration of spinal anesthesia for cesarean section, very distracting because it has to be done at a time when the patient requires complete and uninterrupted attention. This led us to design the device described in this paper.

The authors gratefully acknowledge the technical advice they received from Mr. Francis Gerbasi, MS, CRNA.

## Reference

1. Redick LF. An inflatable wedge for prevention of aortocaval compression during pregnancy. Am J Obstet Gynecol 1979;133:458–9.

# A Single-Unit Device for Differential Lung Ventilation with Only One Anesthesia Machine

Takeyasu Yamamura, MD, Hitoshi Furumido, MD, and Yoshinori Saito, MD

One-lung ventilation during thoracic surgery in the lateral decubitus position occasionally produces hypoxemia, and there has been great interest in methods for maximizing arterial oxygenation (1–3) under such circumstances. Differential lung ventilation is one such method that improves ventilation to the dependent lung and also facilitates surgical manipulation of the nondependent lung. However, differential lung ventilation as generally described requires the simultaneous use of two anesthesia machines and two ventilators. Such complexity severely limits its acceptance into common anesthetic practice (4).

In an attempt to settle these problems, we have developed a single-unit device that allows differential lung ventilation with only one anesthesia machine. The present report describes the technical performance of such a device.

## Structure and Function of the Differential Lung Ventilation Device

A schematic diagram of the differential lung ventilation device (DLVD) is shown in Figure 1. Flow from each of the inspiratory and expiratory limbs of an anesthesia machine can be directed along two paths within the device. Ventilatory paths to and from the nondependent and dependent lung are shown in dashed and solid lines, respectively. Located in the inspiratory path to the nondependent lung, a rotating cylinder *(A)* with a pear-shaped opening plays the leading part in the DLVD. As the cylinder is rotated, the effective opening for the inspired gas changes in size to create greater resistance to flow along this path and thus decrease inspiration to the nondependent lung. When the cylinder is fully rotated, the path is closed. The extent to which ventilation is impeded determines the ventilation of the other lung. On the other hand, expiration from the nondependent lung has low resistance because it escapes through a one-way valve *(C)* remote from the opening (*A*) and does not produce expiratory retardation. In the path to the dependent lung is a two-way stopcock (*B*) that simply opens and closes the airway of this side. It is arranged to permit suctioning and fiberoptic bronchoscopy of this side without discontinuing ventilation of the other side. This can be performed on the other side by setting each of the valve positions conversely. An exchangeable one-way valve (C) isolates the pathway to the nondependent lung from the other during inspiration.

Figure 2 demonstrates how the DLVD controls distribution of ventilation between the two lungs. It is shown that the DLVD offers a range of options for the nondependent lung ventilation going from no ventilation all the way to ventilation exceeding that for the dependent lung. In addition, all of these adjustments can be made without altering the total tidal volume.

The entire device is made of acrylic resin, measures 10 × 14 × 3.5 cm, and weighs 250 g (Fig. 3). Each of the anesthesia machine side ports of the device is fitted with a 22-mm male connector, and each of the patient side ports is fitted with a 15-mm female connector. No point along the entire path within the device is less than 8 mm in diameter, except for the pear-shaped opening, thus the DLVD allows little flow resistance.

## Case 1

A 52-yr-old man with a lung abscess underwent right upper pulmonary lobectomy under thoracic epidural (0.5% bupivacaine) and $N_2O$–$O_2$ anesthesia. After insertion of a double-lumen endobronchial tube (Mallinckrodt, Broncho-Cath), complete ventilatory isolation of each lung was confirmed by fiberoptic bronchoscopy (Olympus, BF-3C4) and by ausculta-

---

A part of this study was presented at the 8th World Congress of Anesthesiologists, Manila, Philippines, January 1984.

Received from the Department of Anesthesia, Sunagawa City Medical Center, Sunagawa, Hokkaido, Japan. Accepted for publication April 29, 1985.

Address correspondence to Dr. Yamamura, Department of Anesthesia, Sunagawa City Medical Center W4 N2, Sunagawa, Hokkaido 073-01 Japan.

© 1985 by the International Anesthesia Research Society

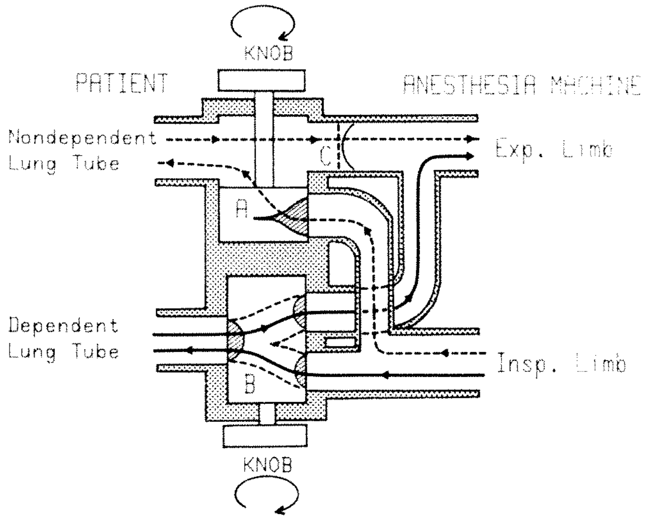


Figure 1. Schematic diagram of the differential lung ventilation device (DLVD). See text for explanations.

tion of the chest. Conventional one-lung ventilation of the dependent lung was instituted with 100% oxygen supplemented with low concentrations (0.4–0.6%) of halothane to provide a quiet surgical field. The blood–gas data obtained 20 min later were pH, 7.33; PaCO$_2$, 43 mm Hg; and PaO$_2$, 72 mm Hg. To improve arterial oxygenation, continuous positive pressure insufflation of the nondependent lung with oxygen at 10 cm H$_2$O was started. The PaO$_2$ increased to 194 mm Hg, but the surgeons complained of the inflated lung. The DLVD was then connected to the anesthesia machine, and differential lung ventilation was started at the tidal ventilation of 400 ml to the dependent lung and 100 ml to the nondependent lung. Blood–gas data obtained 20 min later were pH, 7.34; PaCO$_2$, 39 mm Hg; and PaO$_2$, 287 mm Hg. The small movement of the nondependent lung did not disturb surgical manipulation any longer. The ventilation was successfully controlled throughout the rest of the operative period with the DLVD.

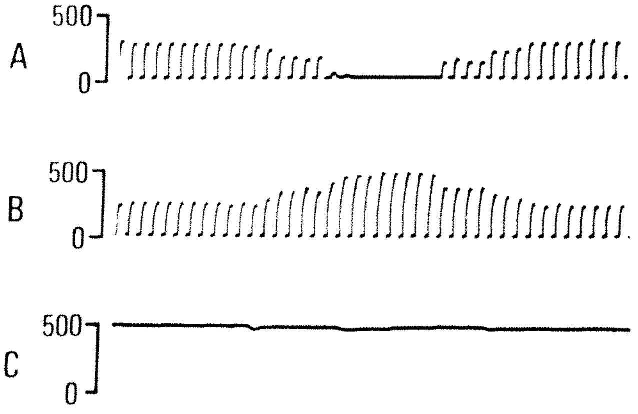


Figure 2. *A*, Volume curves of nondependent lung; *B*, dependent lung; and C, the sum of both lungs; during use of the DLVD. Wave forms were obtained simultaneously by two sets of pneumotach equipments (Criticon, VRP).

## Case 2

A 68-yr-old, 154-cm obese woman weighing 78 kg and suffering from malignant kidney tumor underwent left radical nephrectomy. Preoperative studies, including routine pulmonary function tests, all were within normal limits. Anesthesia was maintained with thoracic epidural anesthesia (0.5% bupivacaine) and 50% nitrous oxide in oxygen. Ventilation was controlled with a single-lumen endotracheal tube. Arterial blood–gas data, obtained 30 min after the initiation of the operation, were pH, 7.34; PaCO$_2$, 42 mm Hg; and PaO$_2$, 56 mm Hg. Because careful check of the anesthesia circuits and auscultation of the chest were negative, the hypoxemia was considered to be caused by severe hypoventilation of the dependent lung due to the kidney position. A double-lumen endobronchial tube (Mallinckrodt, Broncho-Cath) was inserted and connected to the anesthesia machine using our DLVD. The tidal ventilation to each lung, measured with a Wright spirometer with both of the DLVD paths kept open, was 190 ml to the dependent lung and 320 ml to the nondependent lung. In an attempt to improve such an imbalance of ventilation between the two lungs, we adjusted the DLVD to distribute 60% of the ventilation to the dependent lung and the remaining 40% to the nondependent lung. An arterial blood–gas determination obtained 30 min later showed the pH to be 7.36; PaCO$_2$, 38 mm Hg; and PaO$_2$, 188 mm Hg ($F_{IO_2}$, 0.5). The trachea was extubated successfully immediately after the operation, and the postoperative course was uneventful.

## Discussion

Possible types of failure of the DLVD are illustrated in Figure 4. The case in which the inspiratory and expiratory limbs of an anesthesia machine are accidentally reversed is shown in Figure 4(*A*). Although inspiration to the nondependent lung flows circuitously via the two-way stopcock (*B*, solid line) the device still can function while *B* is kept open. When *B* is closed, however, neither lung is supplied by anesthetic gas. Figure 4(*B*) illustrates flow without the one-way valve (C). Because the path to the nondependent lung is not isolated during inspiration, inspired gas flows freely via another path, and the device no longer can control the distribution of the inspiration gas between the two lungs.

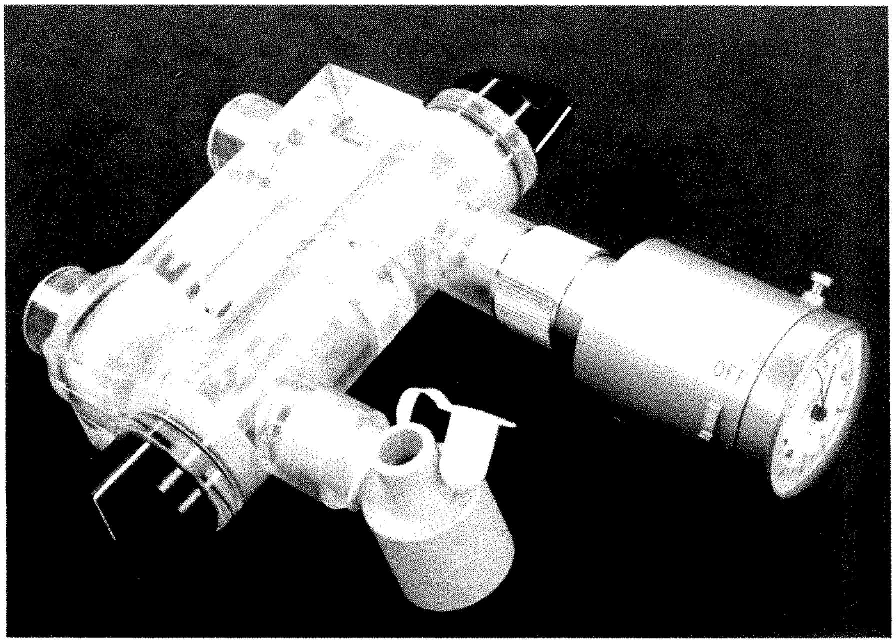
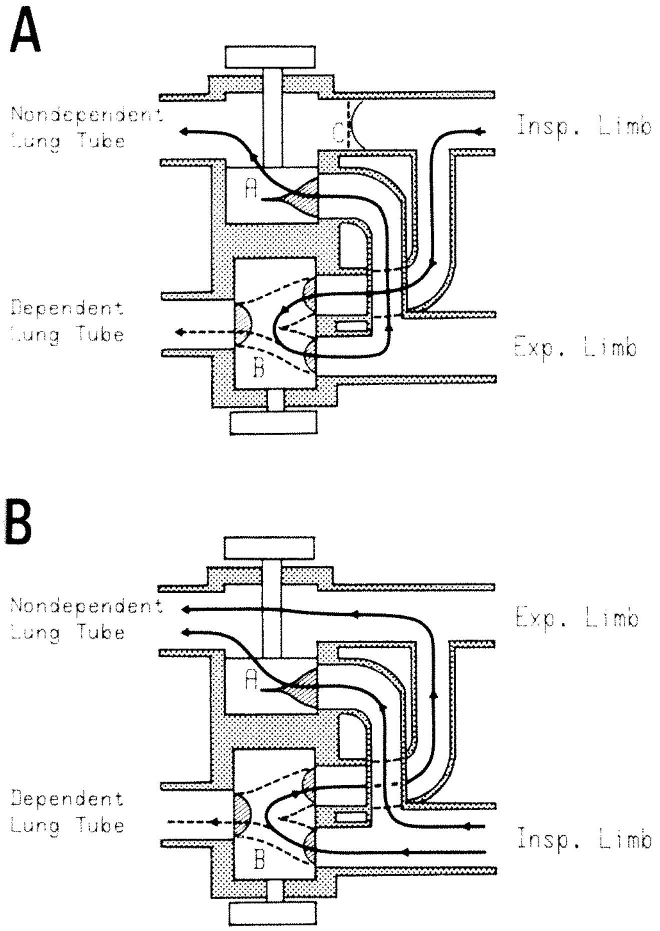


Figure 3. Photograph of the DLVD. A Wright spirometer is placed to one port and a bronchofiberscopic connector to the other.

Figure 4. Types of possible failure of the DLVD. *A*, the inspiratory and expiratory limbs from an anesthesia machine are connected to the DLVD reversely. *B*, the one-way valve at C, which is removable, accidentally is not placed in position. See text for explanation.



Differential lung ventilation has been reported to be quite effective in the respiratory management of patients whose lung disease is predominantly unilateral (5–7). In spite of the expected advantages of this technique for thoracic surgery, few applications have been reported. Without a device such as the DLVD, the complexity of the respiratory circuit prevents acceptance of differential lung ventilation into common anesthetic practice. We believe that the device presented in this report is one solution to the problem. The present design of the DLVD facilitates the performance of differential lung ventilation because it requires only one anesthesia machine. In addition, the device permits simple management of conventional one-lung anesthesia, one-lung fiberoptic bronchoscopy, and suctioning without the need for airway disconnection, clamping or interruption of ventilation. Another advantage of the DLVD is that because only one anesthesia machine is used, ventilatory asynchrony never occurs between the two lungs.

Although the distribution of ventilation between the two lungs can be roughly controlled by visual inspection of the movement of the nondependent lung, a Wright spirometer should be placed between each of the DLVD ports and the double-lumen tube in order to measure the distribution accurately.

## References

1. Capan LM, Turndorf H, Patel C, Ramanathan S, Acinapura A, Chalon J. Optimization of arterial oxygenation during one-lung anesthesia. Anesth Analg 1980;59:847–51.
2. Katz JA, Laverne RG, Fairley B, Thomas AN. Pulmonary oxygen

exchange during endobronchial anesthesia: effect of tidal volume and PEEP. Anesthesiology 1982;56:164–71.

3. Benumaf JL. One-lung ventilation: which lung should be PEEPed? Anesthesiology 1982;56:161–3.
4. Baerendtz S, Klingstedt C. Differential ventilation and selective PEEP during anesthesia in the lateral decubital position. Acta Anaesthesiol Scand 1984;28:252–9.
5. Glass DD, Tonnesen AS, Gabel JC, Arens JF. Therapy of unilateral pulmonary insufficiency with a double lumen endotracheal tube. Crit Care Med 1976;4:323–6.
6. Carlon GC, Ray C Jr, Klein R, Goldiner PL, Miodownik S. Criteria for selective positive end-expiratory pressure and independent synchronized ventilation of each lung. Chest 1978;74:501–7.
7. Gallagher TJ, Banner MJ, Smith RA. A simplified method of independent lung ventilation. Crit Care Med 1980;8:396–9.

ANESTH ANALG 1985;64:1021–5

# Verapamil Potentiation of Neuromuscular Blockade:

## Failure of Reversal with Neostigmine but Prompt Reversal with Edrophonium

Ronald M. Jones, FFARCS, Jeremy N. Cashman, FFARCS, William R. Casson, FFARCS, and Michael P. Broadbent, BA(HONS)

Verapamil is one of a class of drugs that act primarily by interfering with calcium ion flux. These drugs, termed calcium antagonists, are used in a variety of cardiovascular disorders; these include hypertension, angina pectoris, cardiomyopathy, and reentrant supraventricular dysrhythmias. Calcium ions are an essential mediator in the release of acetylcholine at nerve endings. In vitro experiments have suggested that calcium antagonists may potentiate the action of muscle relaxants (1,2). We describe a patient on long-term therapy with verapamil who, 2.5 hr after the administration of 2 mg of pancuronium and 5 mg of tubocurarine, exhibited a marked degree of residual neuromuscular blockade that was resistant to reversal by neostigmine (2.5 mg) but was promptly reversed by edrophonium (28 mg; 0.5 mg·kg$^{-1}$).

## Case Report

A 55-yr-old man, weighing 55 kg, was scheduled to undergo elective cholecystectomy. Two months earlier a diagnosis of hypertrophic obstructive cardiomyopathy had been made and the patient started taking oral verapamil, 40 mg three times daily.

Prior to surgery, preoperative assessment revealed an arterial blood pressure of 140/85 mm Hg and a heart rate of 76 beats/min. There were clinical signs of left ventricular enlargement, but no signs of cardiac failure. The day prior to surgery the hemoglobin concentration was 13.5 g·dl$^{-1}$; plasma concentrations of sodium and potassium were 131 and 4.2 mmol·L$^{-1}$, respectively. The patient had been maintained on oral verapamil, 40 mg three times daily, and had received a dose at 7:00 AM on the morning of surgery (90 min prior to the induction of anesthesia). Premedication consisted of 15 mg papaveretum plus 0.3 mg hyoscine administered intramuscularly 1 hr preoperatively.

Anesthesia was induced with 0.2 mg fentanyl and 150 mg thiopental intravenously, and muscle relaxation was obtained with 2 mg pancuronium and 5 mg tubocurarine. The trachea was intubated and anesthesia maintained with 66% nitrous oxide in oxygen with enflurane up to 2% added to maintain the systolic blood pressure between 100 and 130 mm Hg. Cardiovascular monitoring consisted of an ECG and an automatically cycling sphygmomanometer. The patient's lungs were ventilated using a Nuffield Penlon ventilator via a Bain type breathing system. End-tidal carbon dioxide was monitored used a Hewlett–Packard 47210A Capnometer with an H-P 14360 series sensor. Neuromuscular blockade was monitored with a Vickers Medical Datex Relaxograph NMT100 utilizing a train-of-four pattern of stimulation.

Surgery proceeded uneventfully, although because of chronic inflammation its duration was prolonged (total operating time, 140 min). Total blood loss did not exceed 250 ml, and the patient remained hemodynamically stable throughout the operation. Intraoperatively 1.5 L of Ringer's lactate solution was administered. No further doses of muscle relaxants or analgesics were given, and no other drugs were administered intraoperatively.

At the end of surgery neuromuscular monitoring revealed a marked degree of residual neuromuscular blockade with no return of the third (T3) or fourth (T4) twitch in the train-of-four. At this time the blood pressure was 140/85 mm Hg, heart rate was 68 beats/min (sinus rhythm) and the end-tidal carbon dioxide ten-

---

Received from the Department of Anaesthetics, Guy's Hospital Medical School, The United Medical Schools, University of London, London, United Kingdom. Accepted for publication May 8, 1985.

Address correspondence to Dr. Jones, Department of Anaesthetics, Guy's Hospital Medical School, The United Medical Schools, University of London, London Bridge, London SE1, United Kingdom.

© 1985 by the International Anesthesia Research Society

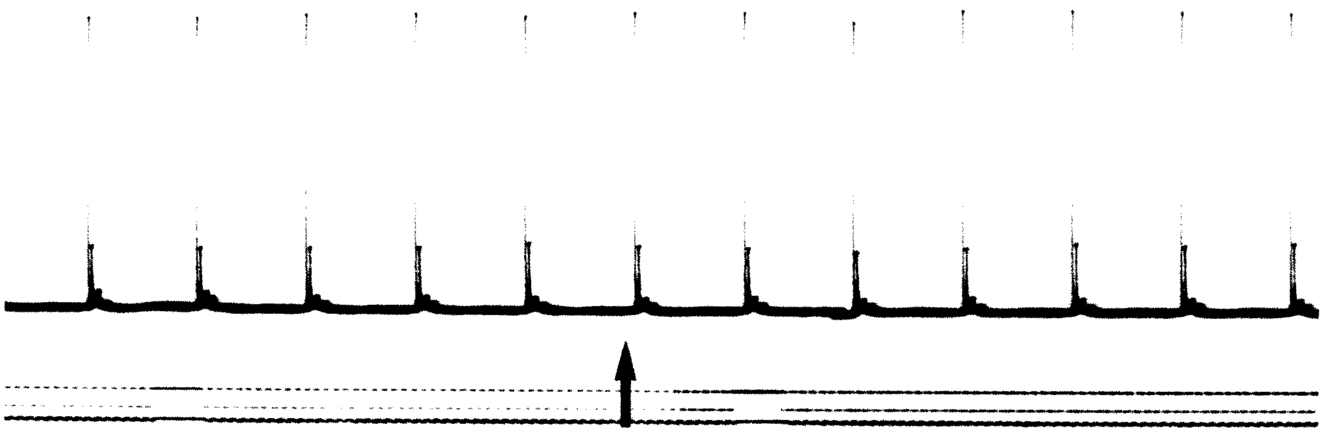


Figure 1. Two and one-half hours after the administration of 2 mg of pancuronium and 5 mg of tubocurarine, a profound degree of residual neuromuscular blockade remained. This was characterized by marked fade of successive stimuli with the second twitch in the train approximately 22% that of the first twitch. Only the first two twitches are clearly defined. Neostigmine, 2.5 mg, plus atropine, 1.2 mg, was administered at the point marked by the arrow.

sion was 39.5 torr (5.2 kPa). Prior to attempting to reverse residual neuromuscular blockade, the degree of paralysis was checked by stimulating the ulnar nerve of the other wrist using supramaximal 0.2-msec impulses in a train-of-four pattern at 2 Hz, repeated every 12 sec (Myotest). The evoked twitch of the adductor pollicis muscle was measured using a Grass force-displacement transducer and a hard copy made using a Devices recorder. The hand and forearm were immobilized in an arm board in a fashion standardized in our unit. Using this system we confirmed the marked degree of neuromuscular blockade present (Fig. 1).

Reversal of residual neuromuscular blockade was first attempted 150 min after induction of anesthesia when 2.5 mg neostigmine and 1.2 mg atropine were given. Six minutes after administering the anticholinesterase there was no change in the degree of neuromuscular blockade present, with no return of T3 or T4 and no significant alteration in the height of T1 or T2 (Figs. 1,2). Edrophonium (28 mg; 0.5 mg$\cdot$kg$^{-1}$) and 0.6 mg atropine were then administered, and within 30 sec a T4 ratio of 1.0 had been achieved (Fig. 3).

The patient was turned on his left side and extubated. In the recovery area he was carefully observed for 3 hr with no evidence of recurarization. During this time the patient could perform sustained head lift and could cough vigorously. Thereafter he made an uncomplicated recovery from anesthesia and surgery.

## Discussion

In the case reported, a marked degree of residual paralysis remained 2.5 hr after the administration of 2 mg pancuronium and 5 mg tubocurarine in a patient on long-term verapamil therapy. The patient had received 40 mg of verapamil 1.5 hr prior to induction of anesthesia. No other drug that might influence neuromuscular transmission had been administered, and the patient was normotensive, normocapnic, and normovolemic. In vitro (1,2) and in vivo (3) animal studies have suggested that calcium antagonists may potentiate the action of both depolarizing and nondepolarizing muscle relaxants. Indeed, conservative doses of relaxant were deliberately used in the case described, and the degree of neuromuscular blockade was carefully monitored because of the known potential for interaction between calcium antagonists and neuromuscular blocking agents. Despite this there remained a marked degree of residual paralysis at the end of surgery. This was not altered to any significant extent by the administration of a standard dose of neostigmine. The complete resistance of the block to

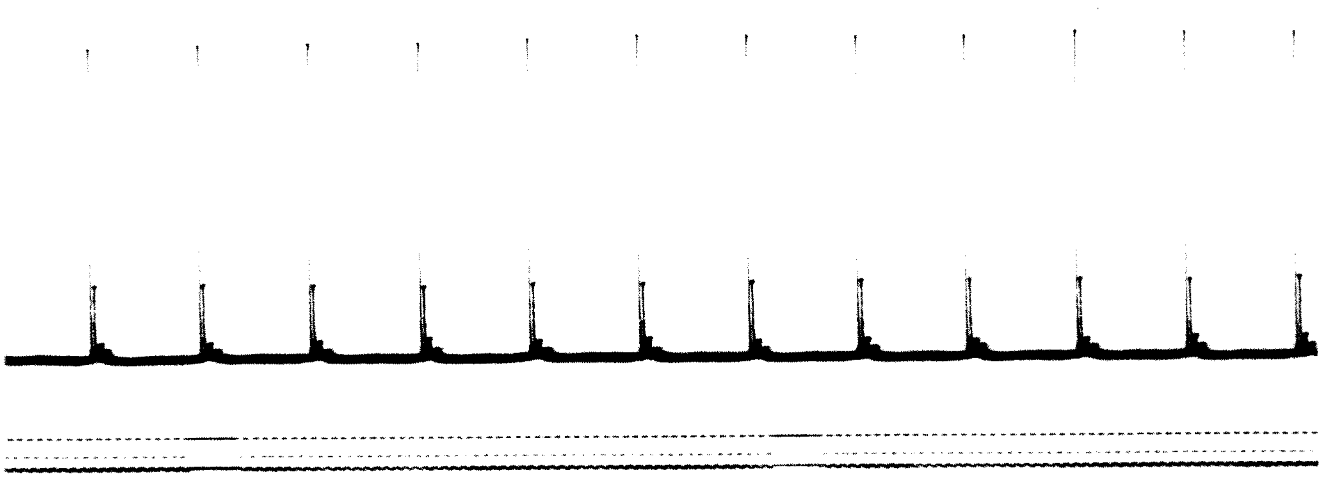


Figure 2. Six minutes after the administration of neostigmine, the degree of block remains virtually unchanged.

evoked reversal using neostigmine, despite the presence of two twitches in the train, was a notable feature of this case. This observation reinforced speculation that the prolonged block was due to an interaction between the muscle relaxant and verapamil as it suggested that the block was quantitatively different from that produced solely by relaxant drugs. We have reported previously that the synthetic acetylcholinesterase inhibitor edrophonium possesses significantly greater antifade properties than neostigmine when used for the evoked reversal of residual neuromuscular blockade (4). In view of the marked fade present at the termination of surgery in this case, and the lack of any effect of neostigmine, it was decided to administer this anticholinesterase agent in a dose of 0.5 mg·kg$^{-1}$. The almost immediate and complete reversal to a T4 ratio of 1.0 was dramatic—and unexpected (Fig. 3). The immediacy and completeness of reversal again suggest that the block was quantitatively different from that produced by relaxants alone.

A mixture of pancuronium and tubocurarine was administered because of the greater cardiovascular stability of mixtures of competitive neuromuscular blocking drugs (5). Pancuronium alone has significant sympathomimetic effects (6) that cause an increase in heart rate and systemic arterial blood pressure, both of which may cause an increase in the degree of outflow obstruction in patients with hypertrophic obstructive cardiomyopathy. Although in vitro (7) and clinical studies (8) have demonstrated that a mixture of pancuronium and tubocurarine produces some potentiation of the intensity of block, this combination does not prolong duration of the block (8). In addition, the lack of a significant response to neostigmine, despite the presence of two twitches in the train-of-four, strongly suggests that this prolonged block was not due to the known wide individual variation in response to relaxant drugs. Vitez and Difrancesco (9) have demonstrated clearly that the neostigmine requirements for pancuronium–tubocurarine combination blocks are the same as those for single-agent blocks.

There has been a previous clinical report in which intravenous verapamil appears to have potentiated the neuromuscular blocking effect of vecuronium (10). The authors also noted that the block was resistant to reversal with neostigmine, but they did not administer edrophonium.

A characteristic feature of the block present in the case reported was the degree of fade present. It is likely that single twitch depression and T4 fade are the result of the interaction of muscle relaxants and other agents that influence neuromuscular transmission, with different sites within the neuromuscular junction. Bowman (11) has discussed the evidence for and against pre- and postsynaptic receptors being responsible for fade. He remarks that although there is evidence in support of and against both possibilities, the weight of evidence is currently in favor of a pre-

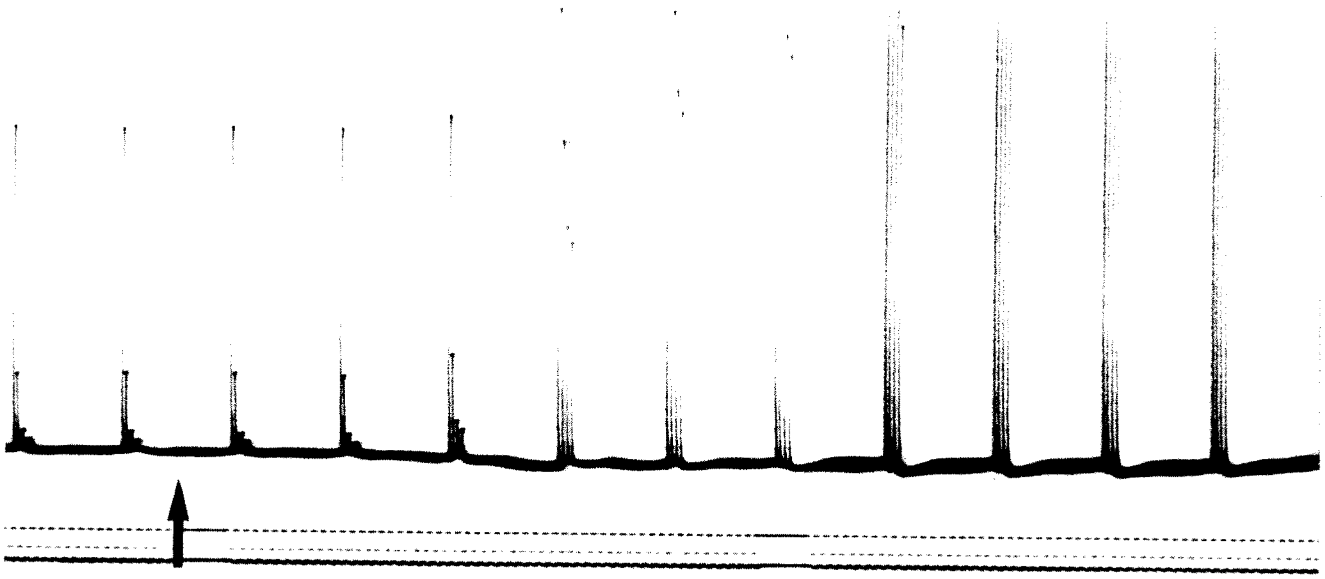


Figure 3. Edrophonium, 28 mg, plus atropine, 0.6 mg, was administered at the point marked by the arrow. Reversal is rapid and complete.

junctional effect. The release of transmitter from nerve terminals, although activated by the descending wave of depolarization, is triggered by the release of calcium ions (12). Current evidence suggests that the change in quantal content of acetylcholine released is proportional to the fourth power of the change in $Ca^{2+}$ concentration (13). Thus decreasing the calcium flux by half would result in a 16-fold decrease in acetylcholine released. The margin of safety is reduced, and fade on repeated stimulation would be more likely to occur. It might be speculated, therefore, that verapamil reduces the mobilization or release of transmitter and hence reduces prejunctional stimulus, an effect that will potentiate the increase in postjunctional threshold caused by muscle relaxants. Whatever the precise mechanism, or site, for the interaction of verapamil and muscle relaxants, it appears that edrophonium may have the ability to rapidly reverse the interference with normal neuromuscular transmission that this combination produces—but that neostigmine may not.

Although the circumstances of this report suggest that the prolonged block was due to an interaction of verapamil and muscle relaxants, it is our experience that many patients receiving long-term verapamil therapy do not demonstrate a clinically significant sensitivity to relaxant drugs. The reason why this proposed drug interaction should occur in some patients but not in others is open to speculation. In any event, we would suggest that patients taking long-term verapamil therapy should be given conservative doses of muscle relaxants and that the degree of blockade should be routinely monitored. Should difficulty with reversal be encountered, edrophonium administration should be considered.

## References

1. Kraynack BJ, Lawson NW, Gintautas J, Tjay HT. Effects of verapamil on indirect muscle twitch response. Anesth Analg 1983;62:827–30.
2. Bikhazi GB, Leung T, Foldes FF. Interaction of neuromuscular-blocking agents with calcium channel blockers (abstract). Anesthesiology 1982;57:A268.
3. Lawson NW, Kraynack BJ, Gintautas J. Neuromuscular and electrocardiographic responses to verapamil in dogs. Anesth Analg 1983;62:50–4.
4. Jones RM, Pearce AC, Williams JP. Recovery characteristics following antagonism of atracurium with neostigmine or edrophonium. Br J Anaesth 1984;56:453–7.
5. Hill AB, Muller BJ, Smith M, Knight PR, Jones RM. Optimum relaxant for high-dose fentanyl induction (abstract). Anesthesiology 1981;55:A208.
6. Kelman GR, Kennedy BR. Cardiovascular effects of pancuronium in man. Br J Anaesth 1971;43:335–8.
7. Pollard BJ, Jones RM. Interactions between tubocurarine, pancuronium and alcuronium demonstrated in the rat phrenic nerve–hemidiaphragm preparation. Br J Anaesth 1983;55:1127–31.
8. Lebowitz PW, Ramsey FM, Savarese JJ, Ali HH. Potentiation of neuromuscular blockade in man produced by combinations

of pancuronium and metocurine or pancuronium and *d*-tubocurarine. Anesth Analg 1980;59:604–9.

9. Vitez TS, Difrancesco LV. Reversal of combination nondepolarized neuromuscular block. Anesth Analg 1983;62:1081–2.

10. van Poorten JR, Dhasmana KM, Kuypers RS, Erdmann W. Verapamil and the reversal of vecuronium neuromuscular blockade. Anesth Analg 1984;63:155–7.

11. Bowman WC. Prejunctional and postjunctional cholinoceptors at the neuromuscular junction. Anesth Analg 1980;59:935–43.

12. Katz B, Miledi R. The effect of calcium on acetylcholine release from motor nerve terminals. Proc Royal Soc Med 1965; 161:496–503.

13. Dodge FA, Rahamimoff R. Co-operative action of calcium ions in transmitter release at the neuromuscular junction. J Physiol (London) 1967;93:419–32.

1026 ANESTH ANALG
1985;64:1026–8

# Gastric Barotrauma:

## A Case Report and Theoretical Considerations

Steven J. Barker, PhD, MD, and Thomas Karagianes, MD

Reported cases of gastric barotrauma have ranged in severity from partial thickness mucosal tears to complete gastric rupture along the lesser curvature. Most barotrauma cases follow cardiopulmonary resuscitation (CPR) and positive pressure ventilation (1,2,6). It has been postulated that the chest compressions may be instrumental in causing gastric rupture in these cases (3). There are only a few descriptions of complete gastric rupture in the absence of chest compression. These have sometimes involved bizarre circumstances, including the insertion of a high pressure oxygen cannula or a fire extinguisher into the mouth (3). We describe a case of gastric barotrauma following attempted bag-and-mask ventilation of an unconscious patient without any application of chest compression.

A common feature of all reported cases has been that the tears occur consistently upon the lesser curvature of the stomach. Autopsies of a series of patients who had undergone CPR revealed partial gastric tears in 10%, all occurring in the lesser curvature (2,4). Experimental studies with cadavers have shown that complete rupture from overpressurization of the stomach also occurs most frequently along the lesser curvature (5). All age and physical status groups are represented in the various case reports, including neonates (3), young adults (1,3), and the elderly (2,4). The tendency for the tears to occur on the lesser curvature is the same in each group. Previous investigators have not provided an explanation for the preponderance of lesser-curvature tears. We present an explanation based upon physical principles that accounts for the consistent involvement of the lesser curvature in gastric barotrauma.

## Case Report

An 87-yr-old man with a history of dysphagia and weight loss due to esophageal dysmotility was scheduled to have a percutaneous gastrostomy performed at bedside by the gastroenterology service. After the intravenous administration of 30 mg of meperidine and 10 mg of diazepam, the patient became unresponsive, apneic, and hypotensive. Positive pressure ventilation was begun with bag and mask, but no chest compressions were employed. Within 5 min after intravenous injection of 1.2 mg of naloxone, the patient awakened with adequate respirations and normal blood pressure. The bedside surgical procedure was cancelled.

During the next 2 hr, the patient developed signs of an acute abdomen. Chest x-ray demonstrated a pneumoperitoneum. The anesthesiology service became involved in his care when he came to surgery for an emergency laparotomy. He was found to have a single full-thickness perforation and several longitudinal serosal tears along the lesser curvature of the stomach. He had no history of preexisting gastric pathology. The lacerations were repaired. The patient tolerated surgery well and had an uneventful recovery.

## Discussion

This case and prior reports share a common feature—the tears occurred along the lesser curvature of the stomach. This predilection for a particular location interested us. We realized that our patient's tear was not due to external force, as chest compressions had not been employed. The tear could not be a consequence of xyphisternal pressure upon an already distended stomach. We must assume that the injury resulted from an internal force, the overinflation of the stomach with gas during positive pressure ventilation.

Why does the overinflated stomach almost always rupture along its lesser curvature? The answer may be found in LaPlace's formula, which relates the sur-

---

Received from the Department of Anesthesiology, University of California Irvine Medical Center and the Surgical Intensive Care Units, University of California San Diego Medical Center. Accepted for publication May 9, 1985.

Address correspondence to Dr. Barker, Department of Anesthesiology, UC Irvine Medical Center, Mail Rte. 81A, 101 City Drive South, Orange, CA 92668.

© 1985 by the International Anesthesia Research Society

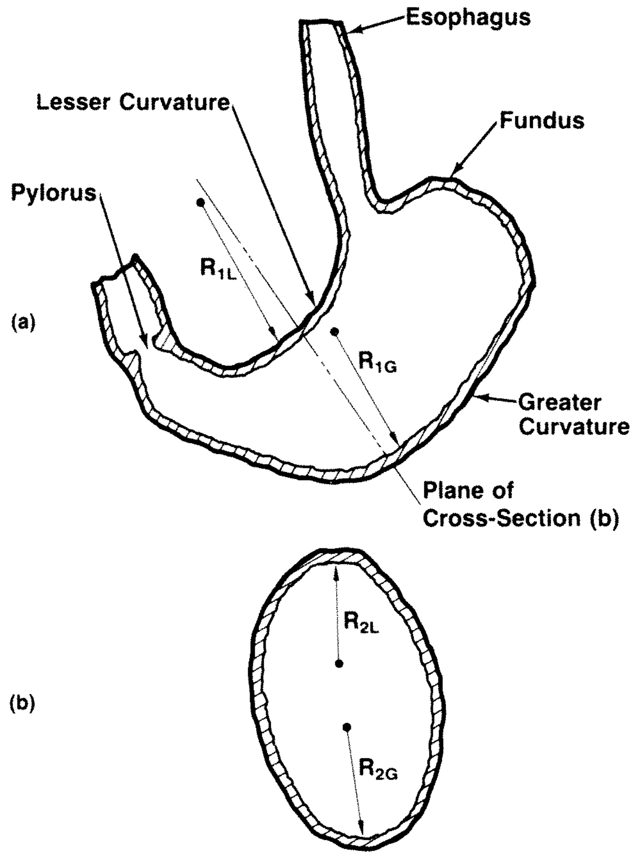


Figure 1. Two cross-section views of the stomach, showing the relationships of the principal radii of curvature in different locations.

face tension of a thin, closed membrane to the pressure within the volume enclosed by the membrane:

$$p = T\left(\frac{1}{R_1} + \frac{1}{R_2}\right). \qquad (1)$$

In this equation $p$ is the static pressure within the enclosed volume, $T$ is the tension in the membrane (in units of force/length), and $R_1$ and $R_2$ are the two principal radii of curvature of the membrane (to be evaluated at each point on the surface of the stomach). Because $p$ is a constant within the enclosed volume, any variations of the radii of curvature $R_1$ and $R_2$ must be counterbalanced by opposing variations in the tension $T$. That is, in regions of the surface where the term in parentheses in equation (1) is smaller, the tension must be correspondingly greater.

Figure 1 depicts two cross-sectional views of the stomach, one in a coronal plane and the second in a saggital plane perpendicular to the long axis of the stomach. In this figure we compare the principal radii of curvature at points on the greater and lesser curvatures of the stomach. (Note that the term "curvature" must unavoidably be used in two senses here; we must distinguish "radii of curvature" from "curvatures of the stomach.") The two radii on the greater curvature are designated $R_{1G}$ and $R_{2G}$, while those on the lesser curvature are $R_{1L}$ and $R_{2L}$. Note that on the greater curvature of the stomach, the radii of curvature are inwardly directed in both views of Figure 1; that is, both $R_{1G}$ and $R_{2G}$ are positive. However, on the lesser curvature of the stomach, the radius of curvature in the coronal view ($R_{1L}$) is directed outward from the enclosed volume, which means this radius is of negative sign. The radius of curvature in the saggital cross section ($R_{2L}$) is again inwardly directed and is therefore positive. This implies that one of the two terms in parentheses in equation (1) will be negative for points on the lesser curvature of the stomach. Therefore, the sum of the reciprocal radii will be significantly smaller on the lesser curvature, and the tension $T$ must be correspondingly greater to balance the opposing pressure from the inside. Thus the lesser curvature of the stomach has been shown to have a greater wall tension than the greater curvature, and as a result will be more likely to rupture from overinflation. In mathemetical terms, defining $T_L$ and $T_G$ as surface tensions on the lesser and greater curvatures respectively:

$$T_L\left(\frac{1}{R_{1L}} + \frac{1}{R_{2L}}\right) = T_G\left(\frac{1}{R_{1G}} + \frac{1}{R_{2G}}\right) = p \qquad (2)$$

$$\frac{1}{R_{1L}} + \frac{1}{R_{2L}} < \frac{1}{R_{1G}} + \frac{1}{R_{2G}} \qquad (3)$$

therefore,

$$T_L > T_G. \qquad (4)$$

The only approximation made in this argument is that we have assumed LaPlace's formula to be valid for the stomach wall. This assumption requires that the radii of curvature be much larger than the stomach wall thickness and that the wall itself has little stiffness (that is, an isolated section of stomach wall will offer little resistance to bending motions). Both of these conditions are closely approximated in the human stomach. The validity of the above argument also depends upon the assumption of no major histological differences between the walls of the lesser and greater curvatures. The strength of the stomach is derived mainly from the three layers of the muscularis externa. One of these, the longitudinal layer, is actually more dense along the lesser curvature and is almost absent on the anterior and posterior surfaces (7). Thus the histological differences would tend to favor an increased rather than a decreased tensile strength along the lesser curvature.

In conclusion, we have given a simple physical explanation for the observation that gastric tears from overpressurization always occur on the lesser curvature. This hypothesis does not rely upon the application of an external force, nor does it require structural or histological differences among different regions of the stomach wall. The predilection for gastric tears to occur along the lesser curvature is a result of the fundamental physical principle of LaPlace's formula and the geometry of the stomach.

It should be mentioned that gastric overpressurization as seen in this case is more likely to occur during relatively unskilled bag-and-mask resuscitation. The likelihood of this occurring also may be connected with the common practice of giving elderly patients "a little anesthesia" for painful procedures performed outside of the operating room.

## References

1. Darke SG, Bloomfield E. Case of complete gastric rupture complicating resuscitation. Br Med J 1975;3:414.
2. Lundberg G, et al. Hemorrhage from gastroesophageal lacerations following closed chest cardiac massage. JAMA 1967;202:123.
3. Cole DS, Burcher SK. Accidental pneumatic rupture of oesophagus and stomach. Lancet 1961;1:24.
4. Anthony PP, Tattersfield AE. Gastric mucosal lacerations after cardiac resuscitation. Br Heart J 1969;31:72.
5. Elders MJ, Hughes ER. Rupture of the stomach: clinical and experimental study. Lancet 1966;86:104.
6. Demos NJ, Poticha SM. Gastric rupture occurring during external cardiac resuscitation. Surgery 1964;55:364.
7. Romanes G., ed. Cunningham's textbook of anatomy. London: Oxford University Press, 1972.

# Letters to the Editor

ANESTH ANALG
1985;64:1029–38

## Subdural Migration of an Epidural Catheter

To the Editor:

The case reported by Hartrick et al. (1) is another reminder of the hazards of aggressive pain management and of the rigorous precautions that are necessary to protect patients from the life-threatening complications of well-meaning analgesic regimens.

Dr. Hartrick's patient accidentally received an infusion of both local anesthetic and a small dose of narcotic (meperidine) into the subdural space. The authors did not report respiratory depression, but it would be interesting to know if any appreciable respiratory depression did follow the sudden arterial hypotension they observed.

We have been slow to develop safe guidelines for all forms of aggressive pain management, where the "therapeutic window" between pain relief and respiratory depression is often alarmingly narrow (2–4). Such guidelines need to be especially rigorous in the case of intraspinal narcotics, for although the results are attractive in terms of excellent pain relief, the risk of insidious and potentially lethal respiratory failure is an inherent danger. The following are suggested as reasonable precautions for epidural narcotics.

Correct catheter placement should be verified by a small dose of local anesthetic prior to each injection of epidural narcotic. Accidental intrathecal injection will be apparent within a few minutes. Signs of accidental subdural injection may take longer to develop. Clearly, continuous infusions of epidural narcotics preclude this particular safety measure, as in the case reported by Hartrick et al. (1).

Respiratory rate is a poor index of impending apnea, and long apneic periods can occur without warning (5). Therefore, patients should be under close surveillance in a recovery ward, ICU, or some appropriate open-ward situation, and in clear view of the nursing station. Single rooms with closed doors are potentially hazardous. Unfortunately, close surveillance in an ICU setting is expensive, and administrative pressures may encourage premature transfer to cheaper but more dangerous quarters.

Apnea monitors are desirable but not infallible. All electrical devices are subject to error, and their presence must be acknowledged for what it is: a back-up system to keen human observation.

Pain relief is a high and worthy aim, but survival of our patients is the most important. Acceptance of a valuable and powerful technique such as epidural narcotic analgesia can only be won by exercising the vigilance and appropriate practices that are necessary to avoid the known dangers (6,7).

Philip R. Bromage, MB, BS, FFARCS
*Department of Anesthesiology*
*University of Colorado Health Sciences Center*
*4200 East Ninth Avenue*
*Denver, Colorado 80262*

### References

1. Hartrick CT, Pither CE, Pai U, Raj PP, Tomsick TA. Subdural migration of an epidural catheter. Anesth Analg 1985;64:175–8.
2. Rigg JRA, Ilsley AH, Vedig AE. Relationship of ventilatory depression to steady state blood pethidine concentrations. Br J Anaesth 1981;56:613–20.
3. Camporesi EM, Nielsen CH, Bromage PR, Durant PAC. Ventilatory $CO_2$ sensitivity after intravenous and epidural morphine in volunteers. Anesth Analg 1983;62:633–40.
4. Gourlay GK, Willis RJ, Wilson PR. Postoperative pain control with methadone: influence of supplementary methadone doses and blood concentration–response relationships. Anesthesiology 1984;61:19–26.
5. Bromage PR, Comporesi EM, Durant PA, Nielsen CH. Influence of epinephrine as an adjuvant to epidural morphine. Anesthesiology 1983;58:257–62.
6. Bromage PR. The price of intraspinal narcotic analgesia: basic constraints. Anesth Analg 1981;60:461–3.
7. Gustafsson LL, Schildt B, Jacobson K. Adverse effects of extradural and intrathecal opiates: report of a nationwide survey in Sweden. Br J Anaesth 1982;54:479–86.

---

## Much Ado About Nothing: Trace Gaseous Metabolites in the Closed Circuit

To the Editor:

Morita et al. (1) demonstrated trace levels of methane and acetone during closed-circuit anesthesia. Personnel in submarines and space vehicles are exposed to these compounds for months with no adverse effects. The air in submarines accumulates flatus as well as expired gas from the crew, whereas a patient is exposed only to the latter. The following lists US Navy concentration limits for acetone and methane in ambient air in submarines (2):

| | 24 hr (ppm) | 90 day (ppm) |
|---|---|---|
| Acetone | 2000 | 30 |
| Methane | 5000 | 5000 |

Morita et al. report a range of 5–229 ppm of methane and 2–13 ppm of acetone. These values are two orders of magnitude below the 24-hr limits and pose no conceivable danger to patients (3).

Hydrogen was not measured by Morita et al. Hydrogen is very diffusible so there is no reason to suspect that it will be retained in the circuit. Nevertheless, the authors' discussion warns that methane and hydrogen will accumulate to explosive levels. The authors did not demonstrate these alarming levels but merely speculated their possible existence after a 14-hr anesthetic.

The authors show small accumulations of nitrogen. These are irrelevant when nitrous oxide is eliminated. The quantitative pharmacokinetics of the closed circuit produces stable, predictable anesthetic depth with potent volatile agents alone. Activated charcoal filters allow rapid emergence without resorting to the use of nitrous oxide (4).

The authors' recommendations are entirely unfounded. If personnel in submarines can breathe these levels of volatile metabolites for months there is no reason to suspect that a patient will be harmed during an average anesthetic. Placing a charcoal filter in line for 1 min will purge the circuit of most contaminants while maintaining a closed system. Methane is poorly adsorbed by charcoal but is easily removed by flushing with three circuit volumes of oxygen. Depending on the machine's flush rate, this will take 30–60 sec. During extremely long procedures, perhaps the circuit should be filtered or flushed every 3 or 4 hr. The circuit would then need to be reprimed with anesthetic agent. Long periods of denitrogenation are unnecessary when nitrous oxide is simply omitted. The open-circuit anesthetist should not grasp at this letter to justify the continued waste and pollution of high-flow anesthesia.

R. K. Baumgarten, MD
W. J. Reynolds, MD, PhD
*630 Alamo Height Blvd.*
*San Antonio, TX 78209*

References

1. Morita S, Latta W, Hambro K, Snider MT. Accumulation of methane, acetone, and nitrogen in the inspired gas during closed-circuit anesthesia. Anesth Analg 1985;64:343–7.
2. Parker JF, West VR. Bioastronautics data book. 2nd ed. Washington, DC: US Government Printing Office, 1973:472.
3. Eger EI. Dragons and other scientific hazards (editorial). Anesthesiology 1979;50:1.
4. Baumgarten RK. Simple charcoal filter for closed circuit anesthesia (letter). Anesthesiology (in press).

---

# Surgically Induced Hypertension in Brain Dead Patients

To the Editor:

I would like to make some historical additions to the bibliography and make a comment on the interesting report concerning surgically induced hypertension in brain dead patients (1). As early as 1891 it was known that as the brain of an animal was sequentially removed in a rostral to caudal direction, pressor responses to noxious stimuli were not abolished until the lower half of the medulla was removed (2). This was more recently confirmed by S.C. Wang et al. by a number of experiments summarized in his book on the brain stem (3). Removal of the entire brain stem abolishes these stimulus-induced responses except in the chronic spinal animal (3) (analogous to the paraplegic patient).

It is known that during anesthesia and surgery the rostral portions of the brain (neocortex and midbrain) can be functional, as manifested by awareness and recall, without simultaneous hypertension, tachycardia or other signs of sympathetic overactivity (4,5). These cardiovascular responses in brain dead patients prove that the reverse condition can also exist, e.g., surgically induced hypertension and tachycardia can be present when the higher brain centers controlling awareness are markedly depressed, even dead.

Merlin D. Larson, MD
*Department of Anesthesia*
*French Hospital—Medical Center*
*4131 Geary Boulevard*
*San Francisco, CA 94118*

References

1. Wetzel RC, Setzer N, Stiff JL, Rogers MC. Hemodynamic responses in brain dead organ donor patients. Anesth Analg 1985;64:125–8.
2. Landois L, Stirling W. A textbook of human physiology. Philadelphia, PA: Blakiston, 1891:855.
3. Wang SC. Physiology and pharmacology of the brain stem. Mount Kisco, NY: Futura, 1980:6–15.
4. Hilgenberg JC. Intraoperative awareness during high dose fentanyl–oxygen anesthesia. Anesthesiology 1981;54:341–2.
5. Saucier N, Walts LF, Moreland JR. Patient awareness during nitrous oxide, oxygen and halothane anesthesia. Anesth Analg 1983;62:239–40.

---

# Movement of the Distal End of the Endotracheal Tube during Flexion and Extension of the Neck

To the Editor:

There appears to be some confusion as to the direction of movement of the tip of an endotracheal tube (ETT) during flexion and extension of the neck. Some anesthesiologists believe that the ETT tip moves upward during flexion and downward during extension; others believe the opposite. The confusion seems to have arisen from the concept that the oropharynx moves "upward" during flexion, and presumably pulls the ETT with it, and vice-versa during extension.

In fact, however, the opposite occurs: the distal tip of the ETT moves *upward* during extension and *downward* during flexion (Fig. 1). This has been well studied by Conrardy et al. (1) who conceptualized the ETT and the vertebral column as concentric arches, one immediately parallel and next to the other. When the neck is flexed, the ETT represents the inner arch with the circumference less than the outer arch (vertebral column). With the ETT length constant and fixed at the mouth, the ETT tip moves toward the carina during the neck flexion, thereby risking endobronchial intubation (Fig. 1(**B**)). When the neck is extended, the ETT represents the outer arch and the circumference becomes greater than the inner arch (vertebral column) so the ETT moves away from the carina (Fig. 1 (**A**)).

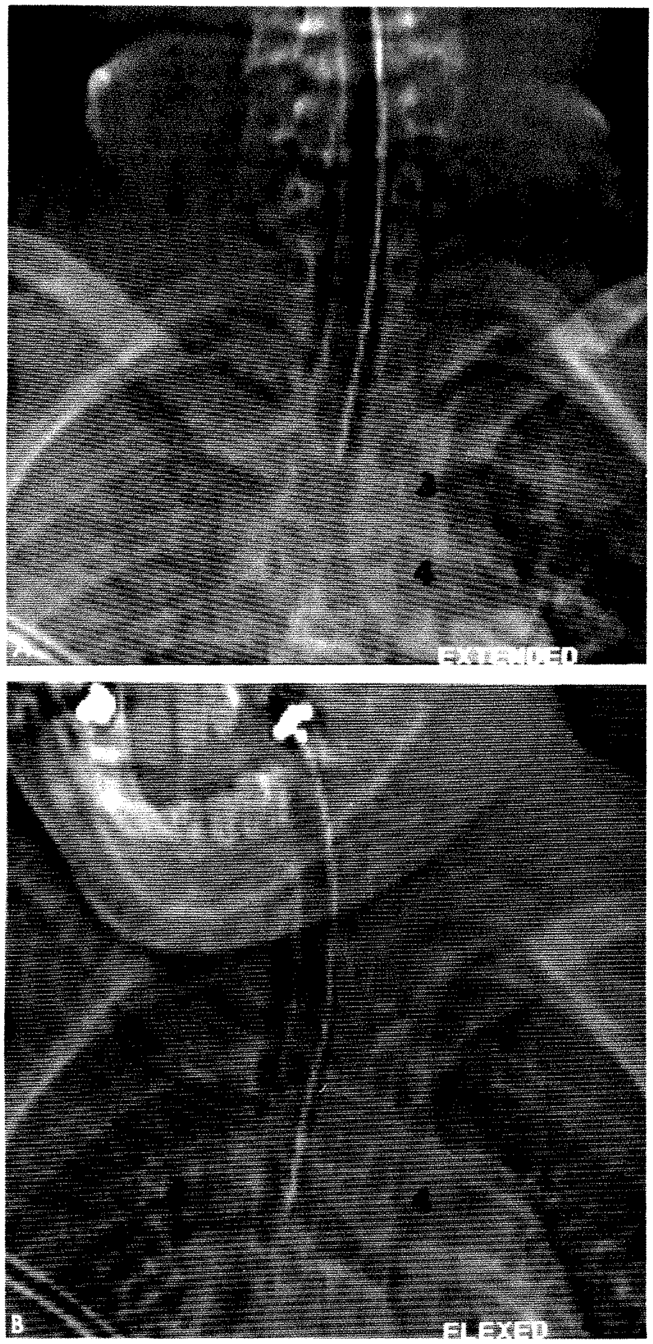


Figure 1. With the neck in the extended position, the ETT tip lies above the carina (**A**), but during flexion (**B**), the tip moves downward toward the right main bronchus. Note the minimal movement of the carina relative to the third and fourth thoracic vertebrae.

Only partially discussed by Conrardy, however, are the positions of the cords and carina with neck flexion and extension. The carina (seen in Fig. 1) only slightly changes position relative to the thoracic vertebrae. The cords, however, (shown in Fig. 2) have clearly moved superiorly from C5 to C4 with neck extension, thereby increasing the distance from cords to carina. The movement of the upper airway, however, is more dramatic with the distance from lips to cords increasing from 13.3 cm to 15.5 cm from flexion to extension.

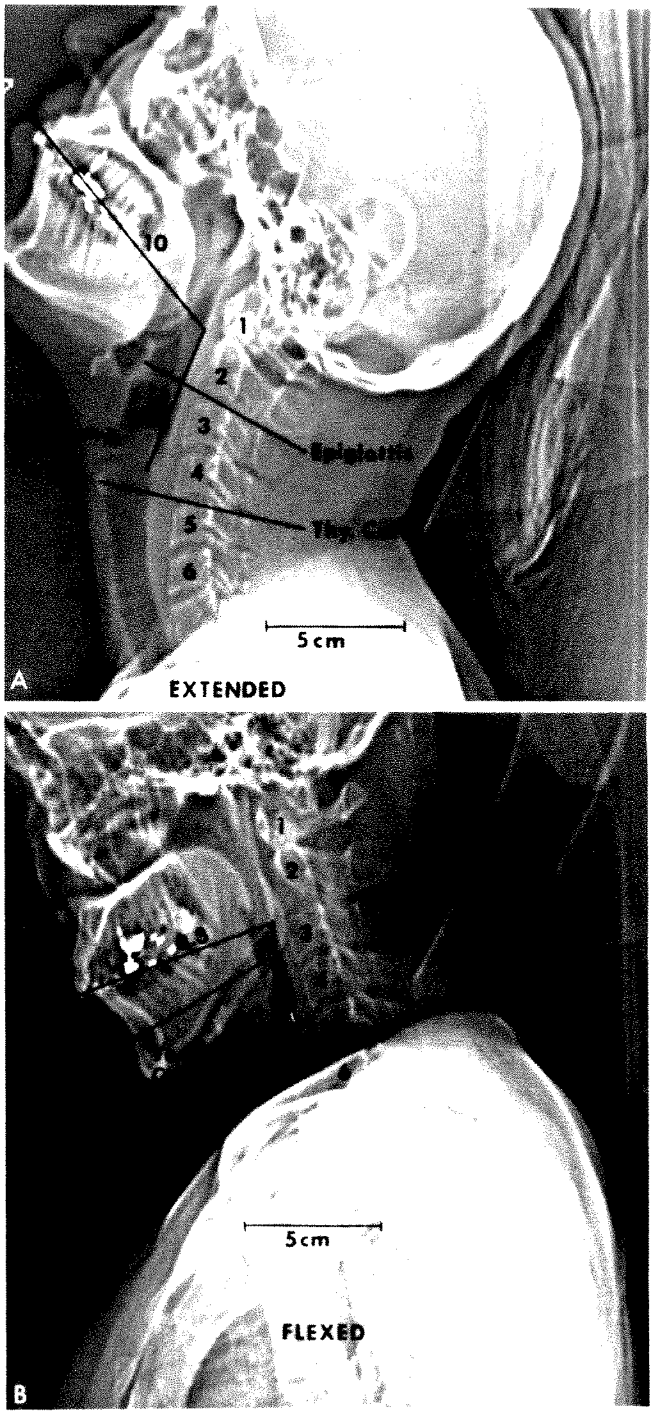


Figure 2. Cervical vertebrae 1–6, upper, and middle airways taken from computed tomography scans of an adult with the neck extended (**A**) and flexed (**B**). Note some upward displacement of the cords as a result of head and neck extension (C5 to C4). Also note the larger increase in distance from incisors → oropharynx → cords during extension. Distances in cm.

Thus while neck extension increases the distance from cords to carina, the distance from cords to lips is increased even more. It is this latter increased distance with the ETT fixed at the lips that will cause the net superior, i.e., rostral, movement of the ETT tip up towards the cords during extension. We hope this explanation helps to clarify how neck extension may risk accidental extubation and neck flexion risks endobronchial intubation when the tube is not in the proper position, i.e., mid-trachea, as suggested by Conrardy et al.

Thomas J. K. Toung, MD
Roger Grayson, MD
James Saklad, MD
Henry Wang, MD
*Departments of Anesthesiology/Critical Care*
*Medicine and Radiology*
*The Johns Hopkins Medical Institutions*
*600 N. Wolfe Street*
*Baltimore, MD 21205*

Reference

1. Conrardy PA, Goodman LR, Lainge F, Singer MM. Alteration of endotracheal tube position. Crit Care Med 1976;4:8–12.

---

# A Simple Method for Improving the Safety of Percutaneous Cannulation of the Internal Jugular Vein

To the Editor:

Percutaneous cannulation of the internal jugular vein is a popular approach for central venous access during cardiac surgery. Of great concern to cardiac anesthesiologists is the possibility of inadvertent cannulation of the carotid artery with a large-bore (8.5 French) introducer-sheath in a patient about to be heparinized (1,2). We have devised a simple method to confirm venous presence of the 18-gauge catheter prior to inserting a guide wire and, subsequently, an introducer-sheath.

A 25-gauge, 2.54-cm needle attached to a 5-ml syringe is used to identify the internal jugular vein. The needle is inserted at the middle of the sternomastoid triangle and angled slightly lateral to the ipsilateral nipple. Once identified, the vein is cannulated with an 18-gauge, over-the-needle type Teflon catheter. A 50-cm straight extension tube with a syringe on the distal end is attached to the hub of the Teflon catheter and blood is withdrawn into the syringe (Fig. 1). The extension set is held in a vertical position, and the syringe is removed. A descending column of blood should be observed in the extension tube. If the column of blood moves up the tube, or remains stationary, the catheter is considered to be in an artery and is promptly removed.

In the first 1000 internal jugular vein cannulations in which this technique was used, there were six instances in which the carotid artery was unknowingly cannulated with the 18-gauge over-the-needle catheter. In each instance, prior to use of the extension tube, the operator was under the impression that the catheter was in the vein because the blood did not spurt out of the 18-gauge catheter and it was not bright red. Our incidence of inadvertent arterial puncture is similar to that reported by Schwartz et al. (1) and by Ellison et al. (3). However, in our series, use of the extension tube test immediately demonstrated arterial presence of the 18-gauge catheter, and insertion of the introducer-sheath into the carotid artery was avoided. We have now used this technique successfully in more than 3000 internal jugular cannulations, and our surgical colleagues have been using it successfully for subclavian vein cannulation as well.

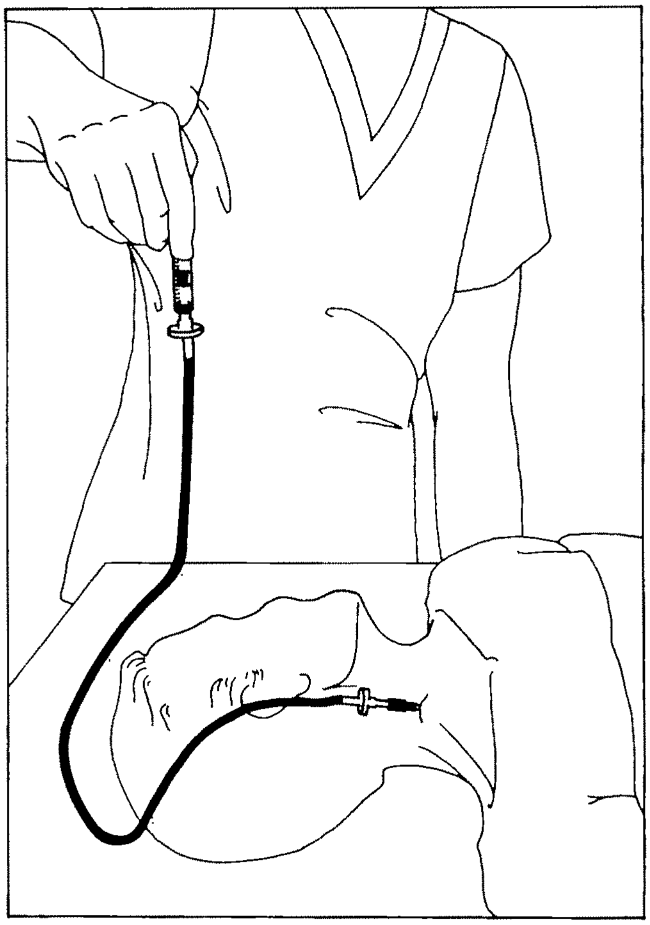


Figure 1. Blood is withdrawn through the extension tube into the syringe.

Recommended techniques to detect carotid artery cannulation include: remove the syringe from the catheter and look for a spurt of blood (4); determine the $P_{O_2}$ of the blood (4); and attach the 18-gauge catheter to a transducer and confirm a venous waveform and pressure (1,3,4). The first technique is unreliable: in our own series it failed in 6 of 1000 catheterizations. The second and third techniques, although reliable, require the assistance of another person if the operator is to maintain an aseptic technique. We think that our technique offers a significant advantage in its combination of simplicity and reliability. It prevents the rare, but potentially life-threatening, complication of inadvertent, large-bore carotid artery cannulation.

Judith A. Fabian, MD
Manoranjan C. Jesudian, MD

*Department of Anesthesiology*
*Medical College of Virginia*
*MCV Station, Box 695*
*Richmond, VA 23298*

References

1. Schwartz AJ, Jobes DR, Greenhow DE, Stephenson LW, Ellison N. Carotid artery puncture with internal jugular cannulation. Anesthesiology 1979;51:S160.
2. Brown CQ. Inadvertent prolonged cannulation of the carotid artery. Anesth Analg 1982;61:150–2.
3. Ellison N, Schwartz AJ, Jobes DR, Greenhow DE, Stephenson LW. Avoidance of carotid artery puncture sequelae during internal jugular cannulation. Anesth Analg 1982;61:181.
4. Hug CC, Jr. Monitoring. In: Miller RD, ed. Anesthesia. New York: Churchill Livingstone, 1981:184–5.

---

# Thoughts on Protamine Toxicity

To the Editor:

I enjoyed reading Horrow's excellent review article (Anesth Analg 1985;64:348–61) on protamine toxicity and would like to comment on several issues. I agree with the author that the "delayed" anaphylactoid reactions reported 30 min or more after the injection of protamine can only tenuously be attributed to protamine administration. An alternative explanation might be that of an anaphylactoid response to fresh frozen plasma (FFP) as was demonstrated in a recent article by Hashim et al. (1). They reported eight patients who developed severe noncardiogenic pulmonary edema 30 min to 4 hr after cardiopulmonary bypass (CPB) associated with FFP administration. Especially impressive was the one patient who developed the same syndrome in the intensive care unit with 50 ml additional FFP. Articles on protamine reactions have not excluded FFP administration as a possible cause of toxic reactions because many institutions routinely give FFP after CPB at about the same time protamine is given. In fact, continuous infusions of FFP have been used to maintain blood volume during protamine reactions (2).

Another subject not discussed in Horrow's review is the possible importance of the source of heparin in mediating heparin–protamine reactions. A recent study comparing cardiovascular effects of protamine in a porcine model with prior administration of either beef lung or porcine mucosal heparin, the source of the heparin was the most significant variable in the hemodynamic response after protamine reversal (3). Porcine heparin was associated with significant decreases in cardiac index and greater increases in pulmonary vascular resistance than was beef heparin. Further studies are needed to determine these differences in humans with different heparin sources.

Finally, the issue of administering steroids, $H_1$ and $H_2$ antagonists to patients at risk for protamine reactions is mentioned. I recently cared for a 56-yr-old man who suffered an anaphylactoid reaction to protamine during heart catheterization three days prior to CABG surgery. He had no known predisposing risk factors for a protamine sensitivity. He was given cimetidine, diphenhydramine, and hydrocortisone before induction of anesthesia and during CPB. Protamine was injected into the aorta over 3 min with almost immediate onset of pulmonary hypertension, low pulmonary artery occlusive pressure, and profound systemic shock requiring open cardiac massage before eventually responding to epinephrine. Certainly intraaortic protamine injection and chemical prophylaxis are not to be relied upon in patients at risk for developing adverse responses to protamine.

Stanley Brauer, MD
*Department of Anesthesiology*
*Loma Linda University*
*Loma Linda, CA 92350*

References

1. Hashim SW, Kay HR, Hammond GL, Kopf GS, Geha AS. Noncardiogenic pulmonary edema after cardiopulmonary bypass. Am J Surg 1984;147:560–3.
2. Olinger GN, Becker RM, Bonchek LI. Noncardiogenic pulmonary edema and peripheral vascular collapse following cardiopulmonary bypass: rare protamine reaction? Ann Thor Surg 1980;29:20–5.
3. Fiser WP, Feuell JE, Hill DE, et al. Cardiovascular effects of protamine sulfate are dependent on the presence and type of circulating heparin. J Thor Cardiovasc Surg 1985;89:63–70.

---

# Ketamine for Treatment of Priapism

To the Editor:

A 44-yr-old, 70-kg man was admitted for treatment with idiopathic priapism of 12 hours' duration. Past medical history was unremarkable and clinical and laboratory evaluation was normal. Priapism was successfully treated with the intravenous administration of ketamine, 2 mg/kg, neostigmine, 1 mg, and diazepam, 5 mg; atropine was not given.

In reviewing the literature on this subject we found the interesting report published by Ravindran et al. (1). These authors, based on Gale's experience (2), administered ketamine for the treatment of priapism in two patients. Gale, the first to describe this use of ketamine, recommended a dose of 1 mg/lb, which seems to have been misinterpreted by Ravindran et al. in their paper, because they say that the dose used by Gale was 0.5 mg/kg. With such a low dose, Ravindran et al. did not obtain satisfactory results; Gale already having reported that 0.5 mg/lb (1.1 mg/kg) was insufficient for treatment of priapism. Ravindran et al. obtained, nevertheless, good results in treatment of priapism, by adding physostigmine, 1.5 mg, to ketamine, 0.5 mg/kg, based on the hypothesis that priapism is the result of reflex autonomic imbalance and physostigmine might be effective by stimulating the peripheral parasympathetic system, which might aid in causing relaxation of vascular sphincters in the corpora cavernosae.

Other authors (3,4) have not, however, subsequently had good results with the ketamine–physostigmine combination, perhaps because physostigmine may antagonize central sedative and anesthetic effects of ketamine (5,6) with the result that the central therapeutic action of ketamine in priapism may be also antagonized by physostigmine. Neostigmine does not cross the blood–brain barrier (7,8), and thus the central antagonism of ketamine would hypothetically be less with neostigmine than with physostigmine, but neostigmine would still have a peripheral parasympathetic stimulation as effective as that of physostigmine.

Although atropine is usually given with ketamine and neostigmine for decreasing the undesirable side effects of both drugs, atropine might counteract desirable muscarinic actions of neostigmine for the treatment of priapism (8). Bradycardia due to neostigmine is counteracted by the sympathomimetic action of ketamine. Atropine thus appears not to be necessary when ketamine–neostigmine combination is administered for treatment of priapism.

In our opinion the combination of ketamine and neostigmine may be more effective than the combination of ketamine and physostigmine, and it could be one of the first therapeutic steps in management of patients with idiopathic priapism.

A. Villalonga, MD
J. Beltran, MD
C. Gomar, MD
M. A. Nalda, MD
*Departmento de Anestesiologia y Reanimacion Hospital Clinic i Provincial*
*Facultad de Medicina*
*Universidad de Barcelona*
*Barcelona, Spain*

## References

1. Ravindran RS, Dryden GE, Somerville GM. Treatment of priapism with ketamine and physostigmine. Anesth Analg 1982;61:705–7.
2. Gale AS. Ketamine prevention of penile turgescence. JAMA 1972;219:1629.
3. Benzon TH, Leventhal JB, Ovassapian A. Ketamine treatment of penile erection in the operating room. Anesth Analg 1983;62:457–8.
4. Lichtor JL. Priapism—a therapeutic challenge. Anesth Analg 1983;62:1136–7.
5. Balmer HGR, Wyte SR. Anatagonism of ketamine by physostigmine. Br J Anaesth 1977;49:510.
6. Toro Matos A, Rendon Platas AM, Avila Valder E, et al. Physostigmine antagonizes ketamine. Anesth Analg 1980;59:764–7.
7. Wood-Smith FG, Vickers MD, Stewart HC. Drugs in anaesthetic practice. London: Butterworths, 1973:9,12.
8. Goodman Gilman A, Goodman LS, Gilman A. The pharmacological basis of therapeutics. 6th Edition. New York: Macmillan, 1980:106.

---

# Myoclonus after Etomidate Anesthesia

To the Editor:

The statement by Laughlin and Newberg (Anesth Analg 1985;64:80–2) that the occurrence of myoclonus on emergence from etomidate anesthesia has not previously been reported is incorrect. This complication was first described in 1979 (1) in patients who had undergone bronchoscopy with etomidate anesthesia, the drug being administered by intermittent injection. Mild to moderate involuntary movements were observed during recovery in seven patients, three of whom had received a small dose of fentanyl at induction. The average duration of bronchoscopy was 22 min and the myoclonus did not last more than 10 min in any patient. The mean dose of etomidate used for maintenance of anesthesia was 0.0192 mg·kg$^{-1}$·min$^{-1}$ when it was used alone and 0.0174 mg·kg$^{-1}$·min$^{-1}$ when preceded by fentanyl. However, the mean dose in those who developed myoclonus was 0.022 mg·kg$^{-1}$·min$^{-1}$. An increase in muscle tone associated with involuntary movement during recovery has also been reported after the steroid anesthetic minaxolone (2,3), but this drug will not be marketed.

The explanation for the appearance of these movements proposed by Laughlin and Newberg appears very reasonable, and we can only assume that suppression of these movements by concomitant use of other central nervous system depressants is the reason for the lack of reports of myoclonus after etomidate. It is a pity that a drug that offers many advantages in terms of immunological safety, cardiovascular stability, and rapid recovery, together with a pharmacokinetic profile that makes it suitable for use by continuous infusion, is beset by a complication that severely limits its use.

Jean Lumley, FFARCS
M. Morgan, FFARCS
*Department of Anaesthetics*
*Royal Postgraduate Medical School*
*Hammersmith Hospital*
*Du Cane Road*
*London, W12 OHS, England*

## References

1. McIntosh BMM, Lumley J, Morgan M, et al. Methohexitone and etomidate for bronchoscopy. Anaesthesia 1979;34:239–44.
2. Punchihewa VG, Morgan M, Lumley J, et al. Initial experience with minaxolone, a water-soluble steroid intravenous anaesthetic agent. Anaesthesia 1980;35:214–7.
3. Dunn GL, Morison DH, McChesney J, et al. An early clinical assessment of the steroid anaesthetic minaxolone. Can Anaesth Soc J 1980;27:140–5.

---

# Aminophylline Antagonism of the Residual Effects of Fentanyl Anesthesia

To the Editor:

We have used aminophylline to reverse the residual effects of fentanyl anesthesia in four patients, with encouraging results. In one patient, surgery was for constrictive pericarditis, in another for patent ductus arteriosus, and in two for mitral stenosis. Total doses of fentanyl were 12, 20, 34, and 30 $\mu$g/kg, respectively. Aminophylline, 2 mg/kg intravenously, restored spontaneous respirations or increased respiratory rate and tidal volume within 9, 20, 5, and 10 min, respectively, and patients regained consciousness after another 10, 20, 5, and 13 min, respectively.

Aminophylline appears to reverse the residual effects of fentanyl anesthesia with no side effects. Its usefulness for this purpose deserves further study.

Wang Ming-de
Ren Zhen-Lin
*Department of Anesthesiology*
*The Chang de Perfective People's Hospital*
*Chang De City, Hunan Province*
*The People's Republic of China*

# Common Sense in Statistical Analyses

To the Editor:

Manchikanti et al. recently provided valuable information concerning the risk factors for aspiration pneumonitis (1). Since the pH of gastric contents is the single most important risk factor, the interpretation of these investigators using pH vs age data warrants comment. The justification for using pH instead of hydrogen ion concentration to compute various statistics is that the calculation of means from pH values is equivalent to computing the geometric mean of the actual hydrogen ion concentrations. Geometric statistics have the advantage of, in effect, assigning less weight to outlier values than does the arithmetic mean. This method is particularly useful when values can differ by a factor of $10^6$, as in the data for gastric hydrogen ion concentration. A single outlier can pull the mean far from the real central tendency (e.g., the arithmetic mean of 7, 8, 8, 9, 9, 10, 1000 is 150, whereas the geometric mean is 16.7). However, if one's primary goal is to measure central tendency, then the median value is almost always a better indication. In the above example the median value is 9.

Why do I make this point? Table 1 shows the mean and median pH values for the three age groups studied by Manchikanti et al. Judging from the mean values, one could conclude that there is a clinically important increase in pH with age. However, the median values indicate there is no change in pH as a function of age. Further, an examination of the authors' Figure 1 shows that the regression line is adversely affected by a relatively small number of high pH values. In the adult age range the regression line is above most of the points, and in the geriatric age range the regression line is even less representative of the data, splitting the difference between what appears to be two distinct groups. If a regression line must be fit to this sort of data, a method such as the least median of squares technique may be preferable (2). This technique results in a virtually horizontal line at a pH near 2.0 regardless of whether pH or actual hydrogen ion concentration is regressed against age.

Table 1. Gastric pH Data

| | Pediatric age group | Adult age group | Geriatric age group |
|---|---|---|---|
| Mean | 1.99 | 2.40 | 3.32 |
| Median | 2.00 | 1.80 | 2.15 |
| Coefficient of variation | 0.18 | 0.65 | 0.63 |

Adapted from Manchikanti et al. (1).

What emerges from Figure 1 displayed in the paper under discussion is that there is increasing scatter with age, and as a result the mean values of pH are successively less reliable indicators of central tendency as verified by the high coefficient of variation for both the adult and geriatric groups (Table 1). A coefficient of variation greater than 0.20 is reason for concern about the usefulness of the data.

All of the above and the important clinical conclusions to be drawn from the authors' Figure 1 are obvious using the technique known as eyeballing. A quick eyeballing of Figure 1 shows about three-quarters of the data points lie below a pH of 2.5 and in none of the three age groups are more than half the data points above a pH of 2.5. Therefore, regardless of age, chances are at least 50:50 that gastric pH will be less than 2.5 and the patient at risk. The authors make this point. However, it is obscured by mean values and regression lines that may lead some to feel that the geriatric patient is at less risk and can be treated differently. Unfortunately, the demands for sophisticated statistical analyses and the availability of complicated statistical software can produce a maze of impressive numbers that frequently miss obvious and important conclusions. It would seem that the current zeal for statistical rigor is occasionally counterproductive.

Denis L. Bourke, MD
*University Hospital*
*Department of Anesthesiology*
*75 East Newton Street*
*Boston, MA 02118*

## References

1. Manchikanti L, Colliver JA, Marrero TC, Roush JR. Assessment of age-related acid aspiration risk factors in pediatric, adult and geriatric patients. Anesth Analg 1985;64:11–7.
2. Rousseeuw PJ. Least median of squares regression. JASA 1984;79:871–80.

In Response:

We thank Dr. Bourke for his comments on our handling of the age–gastric acidity relationship in our paper. Dr. Bourke expresses concern that "one could conclude that there is a clinically important increase in pH with age" that might "lead some to feel that the geriatric patient is at less risk and can be treated differently." We too were concerned and, hence, emphasized in the discussion section that "we have demonstrated that a potential risk of aspiration of acid gastric contents exists at all ages in inpatients undergoing elective surgery despite overnight fasting" and concluded that "theoretically, most patients undergoing surgery under general anesthesia should receive prophylactic therapy to reduce gastric volume and acidity or increase lower esophageal sphincter tone, or both." We also warned that "geriatric patients may seem to be at increased risk of regurgitation of gastric contents as frequency of hiatal hernia, gastroesophageal reflux and decrease in gastric motility increase with age."

In addition, we presented seven different types of results summarizing the relationship between age and gastric acidity in an attempt to communicate clearly its exact nature. Six of the approaches involved grouping patients by age and comparing gastric acidity summary statistics (mean pH, mean $H^+$, pH of mean $H^+$, percent with pH $\leq$ 1.8, percent with pH ≤ 2.5, and percent with pH > 5.0). All six showed geriatric patients to have slightly lower gastric acidity than adults or children. Dr. Bourke expresses concern about the distribution of pH in the three age groups and recommends the use of median pH (although our percent at risk indicators provided the same type of distribution-free description as the median, which is simply the pH with 50% at risk). But even with a distribution-free test (the Kruskal–Wallis analysis of variance by ranks), geriatric patients had significantly higher pH than adults, and adult and pediatric patients did not differ significantly.

Our seventh approach was to present a graph (Fig. 1) that displayed the regression line of pH on age and a plot of the age, pH data points for all 100 patients. Our hope was that the gradual slope of the regression line would communicate the weak, direct relationship between age and pH and that the considerable scatter of points around the regression line would emphasize the weak nature of the relationship. Dr. Bourke recommends the use of a very new technique, least median of squares regression, instead of ordinary least (sum or mean of) squares regression that we used (although the article referenced appeared after our paper had been accepted for publication) (1). Apparently, though, the two techniques produced similar results. The least median of squares technique was said to result "in a virtually horizontal line at a pH near 2.0"; apparently, this means the line had an intercept of 2.0 and a slope near zero. But our results with ordinary least squares regression were quite similar; the intercept was 1.936 and the slope was 0.015 (virtually a horizontal line). To check the stability of our regression findings, we have subsequently analyzed data for 130 controls (adult and geriatric patients, aged 14–87) pooled from five of our previous studies (2–5). The results were virtually identical: the intercept and slope were 1.452 and 0.024, respectively. The slopes (0.015 and 0.024) of our regression lines did not differ significantly ($P = 0.9442$). Thus although the age–gastric acidity relationship is weak and might not provide immediate or direct clinical application, it would seem to be a stable, fundamental relationship of scientific, medical interest.

Admittedly, a cursory reading of our paper (or any paper) could lead to an unwarranted conclusion. But the problem here would not seem to be due to our statistical approach. While we agree with Dr. Bourke that statistical analyses "can produce a maze of impressive numbers that frequently miss obvious and important conclusions" and that "the current zeal for statistical rigor is occasionally counterproductive," the statistical presentation in our paper does not appear to exemplify either of these points. We continue to believe that our presentation accurately communicates the relationship between age and gastric acidity as shown by our data.

Jerry A. Colliver, PhD
*Division of Statistics and Measurement*
*Southern Illinois University School of Medicine*
*Springfield, IL 62702*

Laxmaiah Manchikanti, MD
*Department of Anesthesiology*
*Lourdes Hospital*
*Paducah, KY 42001*

## References

1. Rousseeuw PJ. Least median of squares regression. J Am Stat Assoc 1984;79:887.
2. Manchikanti L, Roush JR. Effect of preanesthetic glycopyrrolate and cimetidine on gastric fluid pH and volume in outpatients. Anesth Analg 1984;53:40–6.
3. Manchikanti L, Colliver JA, Marrero TC, Roush JR. Ranitidine and metoclopramide for prophylaxis of aspiration pneumonitis in elective surgery. Anesth Analg 1984;63:903–10.
4. Manchikanti L, Colliver JA, Roush JR, Canella MG. Evaluation of ranitidine as an oral antacid in outpatient anesthesia. South Med J 1985; in press.
5. Manchikanti L, Grow JR, Colliver JA, Hadley CH, Hohlbein LJ. Bicitra (sodium citrate) and metoclopramide in outpatient anesthesia for prophylaxis against aspiration pneumonitis. Anesthesiology 1985; in press.

---

# Optimization of Oxygenation by CPAP During One-Lung Anesthesia Using Nitrous Oxide:Oxygen

To the Editor:

One-lung ventilation (OLV) results in transpulmonary right-to-left shunt because the nonventilated lung is still perfused. During thoracotomy, Capan et al. (1) have shown that oxygen insufflation into the upper nonventilated lung at 10 cm $H_2O$ CPAP, combined with ZEEP ventilation of the dependent lung using halothane in 100% oxygen can diminish venous admixture and optimize arterial oxygenation. The present report shows that the CPAP technique can also improve oxygenation when nitrous oxide is being used during one-lung ventilation.

The technique was applied in nine adult patients, 30–60 yr, scheduled for resection of pulmonary hydatid cysts or solitary neoplasms. Surgery involved excision of the cyst or lobectomy. Preoperative medication consisted of meperidine, 75 mg, atropine, 0.6 mg, and promethazine, 25 mg injected intramuscularly 1 hr prior to induction. Anesthesia was induced with intravenous thiopental, 5 mg/kg, and succinylcholine, 1.5 mg/kg. After oxygenation, the patient was intubated by a double-lumen bronchial tube (Bronchocath size #35–42). After the appropriate position of the tube was checked and the two lungs were isolated by auscultation of the chest, the tube was firmly fixed in position, and the patient was turned to the lateral decubitus position. Anesthesia was maintained by 50% nitrous oxide:oxygen supplemented by fentanyl, 2 μg/kg, while neuromuscular blockade was continued by the nondepolarizing muscle relaxant alcuronium. Ventilation was controlled throughout the period of investigation by an Ohio Anesthesia ventilator at a rate of 15 per minute, and the minute volume was adjusted to maintain the $Pa_{CO_2}$ ranging between 35 and 45 mm Hg. After 20 min of two-lung ventilation (TLV), arterial blood gas tensions were measured. Ventilation was then limited to the dependent lung using the same concentration of nitrous oxide:oxygen. After 20 min of one-lung ventilation (OLV), blood–gas tensions were measured again. This was followed by the insufflation of 10 L of 50% $N_2O:O_2$ into the upper nonventilated lung at 10 cm $H_2O$ CPAP, while

Table 1. Arterial $P_{O_2}$ (mm Hg) during Ventilation of Both Lungs (TLV), One Lung (OLV), and OLV with CPAP

| Patient | TLV | OLV | OLV + CPAP |
|---|---|---|---|
| 1 | 319 | 125 | 157 |
| 2 | 113 | 73 | 86 |
| 3 | 115 | 65 | 84 |
| 4 | 242 | 86 | 118 |
| 5 | 268 | 60 | 109 |
| 6 | 109 | 70 | 88 |
| 7 | 226 | 72 | 114 |
| 8 | 310 | 159 | 234 |
| 9 | 163 | 97 | 108 |
| Mean | 207.22 | 89.66 | 122 |
| SD | 84.63 | 32.76 | 47.58 |

OLV of the lower lung was continued. The effect of CPAP on the arterial tension was evaluated after 20 min. As shown in Table 1, the mean arterial $P_{O_2}$ during TLV with 50% $N_2O:O_2$ was 207 ± 84 mm Hg. After OLV, the $Pa_{O_2}$ was lowered to 89 ± 35 mm Hg ($P < 0.01$). The application of CPAP to the nonventilated lung significantly increased the $Pa_{O_2}$ to 122 ± 47 mm Hg ($P < 0.01$).

The results of the present report confirm the predictions of Capan et al. that the high $Pa_{O_2}$ achieved with the CPAP technique may permit the use of nitrous oxide during one-lung ventilation (1).

Anis Baraka, MD
Musa Muallem, MD
Maurice Baroody, MD
Robert Mansour, MD
Abdel Nour Sibai, MD
Sania Hroun, MD
Firyal Yamut, MD
*Department of Anesthesiology*
*American University of Beirut*
*Beirut, Lebanon*

Reference

1. Capan L, Turndorf H, Patel C, Ramanathan S, Acinapura A, Chalon J. Optimization of arterial oxygenation during one-lung anesthesia. Anesth Analg 1980;59:847–51.

---

# Precautions in Use of a New Endotracheal Tube for Laser Surgery

To the Editor:

Fire hazard has been recognized as a major complication during $CO_2$ laser surgery (1,2). Xomed Inc. has recently introduced the Laser-Shield cuffed endotracheal tube specifically for use during laser surgery (Fig. 1). This tube is made from silicone with a metallic oxide coating over the cuff and distal two-thirds of the tube. However, a potential fire hazard exists if the cuff of the Laser-Shield endotracheal tube is inflated with air, rather than saline, when used during laser microsurgery of the larynx. The manufacturer's instructions for use of the tube in the package insert explicitly state that the cuff should be inflated with sterile saline or methylene blue and saline. This recommendation is not a mere precaution, but is a necessity to maintain safety for the patient. The saline acts as a heat sump that readily dissipates the high, localized heat of the laser beam as it strikes the cuff. To demonstrate this we directed a beam from a carbon dioxide surgical laser (System 450 by Coherent Medical) onto the cuff of a Laser-Shield endotracheal tube using the laser as suggested by the manufacturer; although in their experiments it was not stated whether their laser beams were directed to the cuff or not. Using a beam pulse of 0.1 sec/pulse in room air at 15 W with a beam diameter between 1–2 mm, nearly 15–20 impacts directed at the same site were required to cause penetration of the cuff when it was inflated with saline. However, with the laser at the same settings one impact was not only sufficient to penetrate the cuff, but even caused momentary ignition of the cuff when inflated with air. This clearly points out the necessity for strict adherence to the manufacturer's instructions of using saline for cuff inflation.

Figure 1. Laser-Shield endotracheal tube by Xomed, with the cuff and the distal half of the tube coated with an unknown metallic oxide.

The manufacturer also cautions against use of this tube in the presence of oxygen concentration greater than 25%. Because many of our patients for laser microsurgery have cardiopulmonary problems that require us to use oxygen concentrations greater than 25%, we have had only limited use of this particular tube in our hospital. At the present time we are utilizing an uncuffed, flexible stainless steel tube (Norton-Devos Tube) (3). In our experience, this tube has proven safe in a wide range of surgical procedures and operating conditions during laser surgery.

Remigio Rubiano, MD
Juei-Ling Chang, MD
Christopher E. Larson, DMD
Robert A. Lawler, MD
Paul Rehkopf
*Departments of Anesthesiology and Ophthalmology*
*Eye and Ear Hospital*
*University Health Center of Pittsburgh*
*Pittsburgh, PA 15213*

References

1. Snow JC, Norton ML, Saluja TS, et al. Fire hazard during $CO_2$ laser microsurgery on the larynx and trachea. Anesth Analg 1976;55:147.
2. Hirshman CA, Smith J. Direct ignition of the endotracheal tube carbon dioxide laser surgery. Arch Otolaryngol 1980;106:639–41.
3. Norton ML, Devos P. New endotracheal tube for laser surgery of the larynx. Ann Otol 1978;87:554–7.

---

# Anesthesia-Related Transient Aphonia and Quadriplegia

To the Editor:

We read with interest the report by Drexler et al. (1) of transient aphonia and quadriplegia associated with epidural anesthesia, but we disagree with their conclusion that this represented a vertebro–basilar transient ischemic attack. We believe a more tenable explanation is that the neurologic abnormalities were psychogenic in origin.

Paralysis of both arms without respiratory involvement suggests either spinal cord involvement at C5 or involvement of both pyramidal tracts (corticospinal tracts) at some higher level within the brain. The former possibility would not account for the aphonia seen in the patient. The observed lack of corticobulbar (supranuclear cranial nerve innervation) findings suggests that the latter possibility is unlikely. Symmetric, bilateral pyramidal lesions in the lower medulla could produce quadriplegia but should also produce tongue weakness (medial medullary syndrome) as cranial nerve XII is closely associated with the pyramidal tracts. The patient described exhibited normal tongue movement. Involvement of the nucleus ambiguous, its derivative cranial nerves IX and X, or both, could result in bilateral vocal cord paralysis, but such lesions should also result in impaired facial sensation (descending tract of cranial nerve V), Horner's syndrome (descending sympathetic pathway), and frequently nystagmus and oscillopsia (vestibular nuclei), the entire complex constituting the lateral medullary syndrome. Furthermore, these structures are considerably removed from the pyramidal tracts; lesions producing aphonia and quadriplegia at this level should involve most of the cross section of the medulla (2). We cannot envision a vascular lesion that could produce quadriplegia and aphonia without numerous other effects.

Even if one ascribes the quadriplegia to a high level of spinal anesthesia and thus unrelated to the presumed transient ischemic attack, one still must confront the issue of which vascular lesions could result in aphonia without production of numerous other findings.

As the authors point out, aphonia and quadriplegia are common hysterical symptoms, and we believe this to be the case in their patient.

W. Davis Parker JR, MD
*Departments of Neurology and Pediatrics*
*University of Colorado School of Medicine*

Kay C. Parker, MD
*Department of Anesthesiology*
*Porter Memorial Hospital*
*Swedish Medical Center*
*Denver, Colorado*

References

1. Drexler H, Zardura S, Shapira Y. Transient aphonia and quadriplegia during epidural anesthesia. Anesth Analg 1985;64:365–6.
2. Adams RD, Victor M. Principles of Neurology, 1st ed. New York: McGraw-Hill, 1977:514.

# Book Reviews

## Endocrinology and the Anaesthetist

T. Oyama, ed. Amsterdam: Elsevier Science Publishers B.V., 1983, 266 pp, $73.00.

*Endocrinology and the Anaesthetist* is volume 11 of a series entitled *Monographs in Anaesthesiology*. It is a well-bound volume, and the layout and typesetting make for easy reading. The 11 chapters cover the endocrine and metabolic responses to surgery, as well as topics as diverse as the thyroid, catecholamines, endorphins, the pituitary, the adrenal, and even myasthenia gravis. A little tabulating reveals that the chapters range from 14 to 39 pages in length, contain 0–14 figures (total of 69), 0–13 tables (total of 41), and are authored by 14 contributors, including seven from the US, two each from Italy, Japan, and Denmark, and one from France. Ten of the authors list affiliations in anesthesia, three in surgery, and one in medicine. Two chapters contain neither a figure nor a table for illustration. Most of the references are from the 1970s, a few from 1980 and 1981, and one from 1982.

Chapter one, "Endocrine Response to General Anesthesia and Surgery," by the editor, is obviously an expanded version of his chapter "Influence of General Anesthesia and Surgical Stress on the Endocrine Function" in the *Contemporary Anesthesia Practice* series of 1980. Although some paragraphs and figures are identical, there is also additional material and an expanded list of references.

Some chapters are succinct, informative, and helpful, for example those on vasopressin and myasthenia. (The latter begins with a paragraph attempting to justify its inclusion in this book!) Unfortunately, as in all multiauthor texts, the style, quality, and depth of presentation vary considerably. Some chapters are too specific and not clinical enough. For example, the chapter on hypophysectomy is used only to explain and promote the author's use of chemical neuroadrenolysis.

There are other annoyances that detract from the value of this book. There are numerous typographic errors. More significant is the occasional lack of information which makes evaluation of a study difficult. For example, the open heart study on page 54 omits data on the intubation (e.g., which relaxant was used, in what dose). A useful chapter on catecholamines is marred by the excessive use of abbreviations. One might also question editing that allows discussion of morphine and fentanyl as "narcotic analgesics," but sufentanyl and alfentanyl as "narcotic agonists–antagonists" (p 249).

More significantly, the value of the book is limited by a grossly inadequate, inconsistent, and incomplete index covering only 1½ pages. Why, for example, should alfentanyl and sufentanyl be indexed but not fentanyl? All three are discussed on the same page (249), and fentanyl is discussed in greater detail. On pages 236–7 we find 17 lines devoted to guanethidine, 4½ lines to bretylium, and seven lines to reserpine, yet only the last two make the index. There is no mention of thiopental or any other barbiturates in the index, although they are mentioned in more than one place in the text. Similarly there is no mention of diazepam, although two-thirds of page 250 is devoted to it. The chapter on diabetes discusses cortisol in normal man on page 96; that page is indexed, yet a full page (106) devoted to cortisol in diabetics is not indexed.

This book might have been useful either as a clinical text supplement or as a reference source. It fails to satisfy either goal. It does not contain enough clinically useful, well presented material to justify its inclusion in every physician's collection; it fails as a reference source because of its poor index.

Arthur J. Klowden, MD
*Illinois Masonic Medical Center*
*The University of Illinois School of Medicine*
*The Shriner's Hospital for Crippled Children*
*Chicago, IL 60680*

---

## Cardiovascular Anesthesia

Carol L. Lake. New York: Springer-Verlag, 1985, 467 pp, $49.50.

There is no doubt that *Cardiovascular Anesthesia* by Carol Lake, MD, achieves the goals stated in the preface. The book covers all aspects of a cardiac surgical patient's perioperative experiences, and the principles developed certainly are applicable to noncardiac patients as well. This latest entry in the cardiac anesthesia field is unique in that it is a single-authored text. The well organized, clearly written, comprehensive chapters reflect Dr. Lake's detailed, meticulous approach to patient care. The consistency of style and lack of repetition enhance readability.

Although single-authored, the text presents multiple points of view supported by numerous up-to-date references, almost all of which are from the late 1970s and 1980s. The typeface is clean and bright. Tables and figures are well-designed and clearly labeled. A comprehensive index and extensive use of subheadings in each chapter make it easy to locate specific material. Features that would have been useful but which are not included are a table of abbreviations used and, because references are so extensive, an index to authors cited. A chapter on the historical aspects of cardiovascular anesthesia would have added an extra dimension to the book. The book does have misspellings; two that I noticed are in the Table of Contents, Chapter One, "Cardivascular" and on page 375 in the running head, "cardiovasculr."

In summary, Dr. Lake's *Cardiovascular Anesthesia* is an impressive source of information for all those involved in the care of cardiac patients. At $49.50 it is a real bargain.

William A. Lell, MD
A. J. Wright, MLS
*Department of Anesthesiology*
*University of Alabama Medical Center*
*Birmingham, AL 35233*

---

## Books Received

Receipt of the following books from their publishers is acknowledged with thanks. Selected books from this list will be reviewed in Anesthesia and Analgesia.

Recent Advances in Anesthesia and Analgesia. R. S. Atkinson and A. P. Adams, eds. New York: Churchill-Livingstone, 1985, 231 pp, $25.00.

Body and Self. G. Bloch. Los Altos, California: Wm Kauffman, Inc., 1985, 313 pp, $15.95.

Case Studies in Critical Care Medicine. R. D. Cane and B. A. Shapiro, eds. Chicago: Yearbook Medical Publishers, Inc., 1985, 262 pp, $29.95.

High Frequency Ventilation in Intensive Care and During Surgery. Vol. 26, Lung Biology in Health and Disease. G. C. Carlon and W. S. Howland, eds. New York: Marcel Dekker, 1985, 297 pp, $59.75 (US and Canada), $71.50 (all other countries).

L'Enfant Paralyse. A. Dimegio, A. Auriach, and L. Simon. Paris: Mason, 1985, 216 pp, 190 francs.

Surfactante Pulmonar. J. P. Drummond. Rio de Janeriro, Brazil: Colina Edetora, 1985.

Nitrous Oxide/$N_2O$. E. I. Eger II, ed. New York: Elsevier, 1985, 369 pp, $37.50.

Handbook of Physiology, Section 3. The Respiratory System, vol. 1. Circulation and Nonrespiratory Function. Bethesda, Maryland: American Physiological Society, 1985, 572 pp, $136.00.

Reanimation et Medicine D'Urgence. G. Francis, M. Posvert, and P. Bouletreape. Paris: Masson, 1985.

Practical Guide to the Care of the Surgical Patient, 2nd ed. R. L. McEntyre. St. Louis, Missouri: C. V. Mosby, 1984, 280 pp, $16.95.

Practical Guide to the Care of the Surgical Patient, 2nd ed. R. L. McEntyre. St. Louis, Missouri: C. V. Mosby, 1984, 280 pp, $16.95.

Handbook of Regional Anesthesia. P. P. Raj, ed. New York: Churchill-Livingstone, 1985, 285 pp, $40.00.

The Resident's Friend. B. I. Rose. Sunnyvale, California: Byte-Omega, Computer software and instruction manual, $99.00.

La Douleur Chronique. L. Simon, B. Roquefeuil, and J. Pellisier, eds. Paris: Masson, 1985, 272 pp.

Acute Pain. G. Smith and B. G. Covino. Stoneham, Massachusetts: Butterworths, 1984, 412 pp, $59.95.

Advances in Anesthesia, vol. 2. R. K. Stoelting, P. G. Barash, and T. J. Gallagher, eds. Chicago: Yearbook Medical Publishers, 1985, $55.95.

Cerebral Death, 3rd edition. E. A. Walker. Baltimore-Munich:Urba & Schwarzenberg, 1985, 206 pp, $34.50.

Textbook of Pain. P. D. Wall and R. Melzack, eds. New York: Churchill-Livingston, 1984, 864 pp, $105.00.

Acute Respiratory Failure. W. M. Zapol and K. J. Falke, eds. New York: Marcel Dekker, 1985, 674 pp, $99.75.

---

## ERRATUM

Swen J, Gencarelli PJ, Koot HWJ. Vecuronium infusion dose requirements during fentanyl and halothane anesthesia in humans. Volume 64, Number 4, April 1985

Page 413, column 2, line 4 from the bottom
CHANGE . . . $mg \cdot kg^{-1} \cdot hr^{-1}$
TO READ . . . $\mu g \cdot kg^{-1} \cdot hr^{-1}$

Page 414, column 1, line 1
CHANGE . . . $mg \cdot kg^{-1} \cdot hr^{-1}$
TO READ . . . $\mu g \cdot kg^{-1} \cdot hr^{-1}$

# A Guide for Authors

## Manuscripts should be sent to:

Nicholas M. Greene, MD
Editor in Chief
*Anesthesia and Analgesia*
Yale University School of Medicine
333 Cedar Street, New Haven, CT 06510

### Editorial Policies

*Anesthesia and Analgesia* is the oldest publication for the specialty of anesthesiology. Established 60 years ago, the Journal is the official voice of the International Anesthesia Research Society. It publishes original articles, clinical reports, technical communications, review articles, and letters to the editor to provide researchers, practicing physicians, and allied medical personnel in anesthesiology and related disciplines with monthly information to keep them current with the latest issues and advances in the field.

All papers are reviewed by three or more referees. Acceptance is based upon significance, originality, and validity of the material presented. Only one copy of the articles not accepted for publication will be returned to the author.

All papers will be edited for clarity, style, factual accuracy, internal logic, and grammar. The submitted manuscript should be accompanied by a covering letter that must include a statement to the editor about all submissions and previous reports that might be regarded as prior or duplicate publication of the same, or very similar, work. The title page and abstract of such material should be included with the submitted manuscript to help the editor decide how to deal with the matter.

Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," reprinted in *Annals of Internal Medicine* 1982;96:766-71 and *Lancet* 1982;284:1766-70.

Use the checklist given below for preparation of manuscripts:

### General

☐ Original articles describe in 3000 words or less clinical or laboratory investigations.

☐ Clinical reports describe in 1000 words or less either new and instructive case reports or anesthetic techniques and equipment of demonstrable originality, usefulness, and safety.

☐ Technical communications are papers that deal with instrumentation and analytic techniques.

☐ Review articles of 2500 to 4000 words collate, describe, and evaluate previously published material to aid in evaluating new concepts.

☐ Letters to the editor, less than 300 words in length, include brief constructive comments concerning previously published articles or brief notations of general interest. The manuscripts must be double spaced, and a title and three copies must be provided.

☐ Type manuscripts on white bond paper, 216 by 279 mm (8-1/2 by 11 in.) or ISO A4 (212 by 297 mm) with margins of at least 25 mm (1 in) using double spacing throughout.

☐ Begin each of the following sections on separate pages: title page, abstract and key words, text, acknowledgments, references, tables (each table, complete with title and footnotes, should be on a separate page), and legends. Type only on one side of the paper and number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.

☐ Submit three copies of manuscript and figures in a heavy paper envelope. Submitted manuscripts should be accompanied by a covering letter, and permissions to reproduce previously published materials or to use illustrations that may identify subjects.

☐ Authors should keep copies of everything submitted.

### Title Page

☐ The title page should contain the title of the article, which should be concise but informative;

☐ A short running head or footline of no more than 40 characters (count letters and spaces) placed at the foot of the title page and identified;

☐ First name, middle initial, and last name of each author, with highest academic degree(s);

☐ Name of department(s) and institution(s) to which the work should be attributed;

☐ Disclaimers, if applicable;

☐ Name and address of author responsible for correspondence about the manuscript;

☐ Name and address of author to whom requests for reprints should be addressed, or a statement that reprints will not be available from the author;

☐ The source(s) of support in the form of grants.

### Abstract and Key Words

☐ The second page should carry an abstract of not more than 150 words.

☐ The abstract should state the purposes of the study or investigation, basic procedures (study subjects or experimental animals; observational and analytic methods), main findings (give specific data and their statistical significance, if possible), and the principal conclusions. Emphasize new and important aspects of the study or observations.

☐ Define all abbreviations except those approved by the International System of Units.

☐ Key (indexing) terms: Below the abstract, provide (and identify as such) 3 to 10 key words or short phrases that will assist indexers in cross indexing the article and that may be published with the abstract.

### Text

☐ The text of observational and experimental articles is usually—but not necessarily—divided into sections with the headings Introduction, Methods, Results, and Discussion. Long articles may need subheadings within some sections to clarify their content, especially in the Results and Discussion sections.

☐ Case reports, reviews, and editorials do not require the above sections.

☐ *Introduction:* Clearly state the purpose of the article. Summarize the rationale for the study or observation. Give only strictly pertinent references, and do not review the subject extensively.

☐ *Methods:* Describe the selection of observational or experimental subjects (patients or experimental animals, including controls) clearly. Identify the methods, apparatus (manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions for methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations.

☐ Identify precisely all drugs and chemicals used, including generic name(s), dosage(s), and route(s) of administration.

☐ Do not use patients' names, initials, or hospital numbers.

☐ Include numbers of observations and the statistical significance of the findings when appropriate. Detailed statistical analyses, mathematical derivations, and the like may sometimes be suitably presented in the form of one or more appendixes.

☐ *Results:* Present the results in logical sequence in the text, tables, and illustrations. Do not repeat in the text all the data in the tables and/or illustrations; emphasize or summarize only important observations.

☐ *Discussion:* Emphasize the new and important aspects of the study and conclusions that follow from them. Do not repeat in detail data given in the Results section. Include in the Discussion the implications of the findings and their limitations and relate the observations to other relevant studies. Link the conclusions with goals of the study but avoid unqualified statements and conclusions not completely supported by the data. Avoid claiming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly label them as such.

☐ Recommendations, when appropriate, may be included.

### References

☐ Number references consecutively in the order in which they are first mentioned in the text, except in review articles when references may be arranged alphabetically.

☐ Identify references in text, tables, and legends by arabic numerals (in parentheses, on line).

☐ Use the style of the examples below, which are based on the format used by the US National Library of Medicine in *Index Medicus.*

☐ The titles of journals must be abbreviated according to the style used in *Index Medicus.*

☐ Try to avoid using abstracts as references; "unpublished observations" and "personal communications" may not be used as references although references to written, not verbal, communications may be inserted (in parentheses) in the text. Information from manuscripts submitted but not yet accepted should be cited in the text as "unpublished observations" (in parentheses). Authors citing as references articles from their own group that are in press and that have a bearing on the paper submitted should enclose 3 copies of an abstract of such in press materials.

☐ References must be verified by the author(s) against the original documents.

☐ Examples of correct forms of references are given below:

*Journals:*

1. *Standard Journal Articles* (List all the authors when six or less; when seven or more, list only the first three and add et al.)
   You CH, Lee KY, Chey RY, Menguy R. Electrogastrographic study of patients with unexplained nausea, bloating and vomiting. Gastroenterology 1980;79:311-4.
2. *Corporate Author*
   The Royal Marsden Hospital Bone-Marrow Transplantation Team. Failure of syngeneic bone-marrow graft without preconditioning in post-hepatitis marrow aplasia. Lancet 1977;2: 242-4.
3. *No Author Given*
   Anonymous. Coffee drinking and cancer of the pancreas (Editorial). Br Med J 1981;283:628.
4. *Journal Supplement*
   Mastri AR. Neuropathy of diabetic neurogenic bladder. Ann Intern Med 1980;92(2 Pt 2):316-8.

   Frumin AM, Nussbaum J, Esposito M. Functional asplenia: demonstration of splenic activity by bone marrow scan (Abstract). Blood 1979;54(suppl 1):26a.
5. *Journal Paginated by Issue*
   Seaman WB. The case of the pancreatic pseudocyst. Hosp Pract 1981;16(Sep):24-5.

*Books and Other Monographs:*

6. *Personal Author(s)*
   Eisen HN. Immunology: an introduction to molecular and cellular principles of the immune response. 5th ed. New York: Harper and Row, 1974:406.
7. *Editor, Compiler, Chairman as Author*
   Dausset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.
8. *Chapter in a Book*
   Weinstein L, Swartz, NM. Pathogenic properties of invading microorganisms. In: Sodeman WA, Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457-72.
9. *Published Proceedings Paper*
   DuPont B. Bone marrow transplantation in severe combined immunodeficiency with an unrelated MLC compatible donor. In: White HJ, Smith R, eds. Proceedings of the third annual meeting of the International Society for Experimental Hematology. Houston: International Society for Experimental Hematology, 1974:44-6.
10. *Monograph in a Series*
   Hunninghake GW, Gadek JE, Szapiel SV, et al. The human alveolar macrophage. In: Harris CC, ed. Cultured human cells and tissues in biomedical research. New York: Academic Press, 1980:54-6. (Stoner GD, ed. Methods and perspectives in cell biology; vol. 1).
11. *Agency Publication*
   Ranofsky AL. Surgical operations in short-stay hospitals: United States—1975. Hyattsville, Maryland: National Center for Health Statistics, 1978; DHEW publication no. (PHS) 78-1785. (Vital and health statistics; series 13; no. 34).
12. *Dissertation or Thesis*
   Cairns RB. Infrared spectroscopic studies of solid oxygen (Dissertation). Berkeley, California: University of California, 1965. 156 pp.

### Tables

☐ Type each table double spaced on a separate sheet. Do not submit tables as photographs.

☐ Number tables consecutively and supply a brief title for each. Give each column a short or abbreviated heading.

☐ Place explanatory matter in footnotes, not in the heading. Explain in footnotes all nonstandard abbreviations that are used in each table. For footnotes, use lowercase italicized letters in alphabetical order.

☐ Do not use internal horizontal or vertical rules.

☐ Cite each table in the text in consecutive order.

☐ If data are used from another published or unpublished source, obtain permission and acknowledge fully.

☐ The editor, on accepting a manuscript, may recommend that additional tables containing important backup data too extensive to publish be deposited with the National Auxiliary Publications Service or made available by the author(s). In that event, an appropriate statement will be added to the text. Submit such tables for consideration with the manuscript.

### Illustrations

☐ Submit three complete sets of figures. Figures should be professionally drawn and photographed; freehand or typewritten lettering is unacceptable.

☐ Instead of original drawings, roentgenograms, or other material send sharp, unmounted, glossy black-and-white photographic prints, usually 127 by 173 mm (5 by 7 in) but no larger than 203 by 254 mm (8 by 10 in).

☐ Letters, numbers, and symbols should be clear and even throughout and of sufficient size that, when reduced for publication, each item will still be legible. Titles and detailed explanations belong in the legends for illustrations, not on the illustrations themselves.

☐ Each figure must have a label pasted on its back indicating the number of the figure, the names of the authors, and the top of the figure. Do not write on the back of the figures or mount them on cardboard, or scratch or mar them by using paper clips. Do not bend figures.

- ☐ Photomicrographs must have internal scale markers. Symbols, arrows, or letters used in the photomicrographs should contrast with the background.
- ☐ If photographs of patients are used, either the subjects must not be identifiable or their pictures must be accompanied by written permission to use the photograph.
- ☐ Cite each figure in the text in consecutive order. If a figure has been published, acknowledge the original source and submit written permission from the copyright holder to reproduce the material. Permission is required, regardless of authorship or publisher, except for documents in the public domain.
- ☐ For illustrations in color, supply color negatives or positive transparencies and, when necessary, accompanying drawings marked to indicate the region to be reproduced; in addition, send two positive color prints to assist editors in making recommendations. Illustrations will be published in color only if the author pays for the extra cost.

## Legends for Illustration

- ☐ Type legends for illustrations double spaced starting on a separate page, with arabic numerals corresponding to the illustrations.
- ☐ When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend. Explain internal scale and identify method of staining in photomicrographs.

## Abbreviations

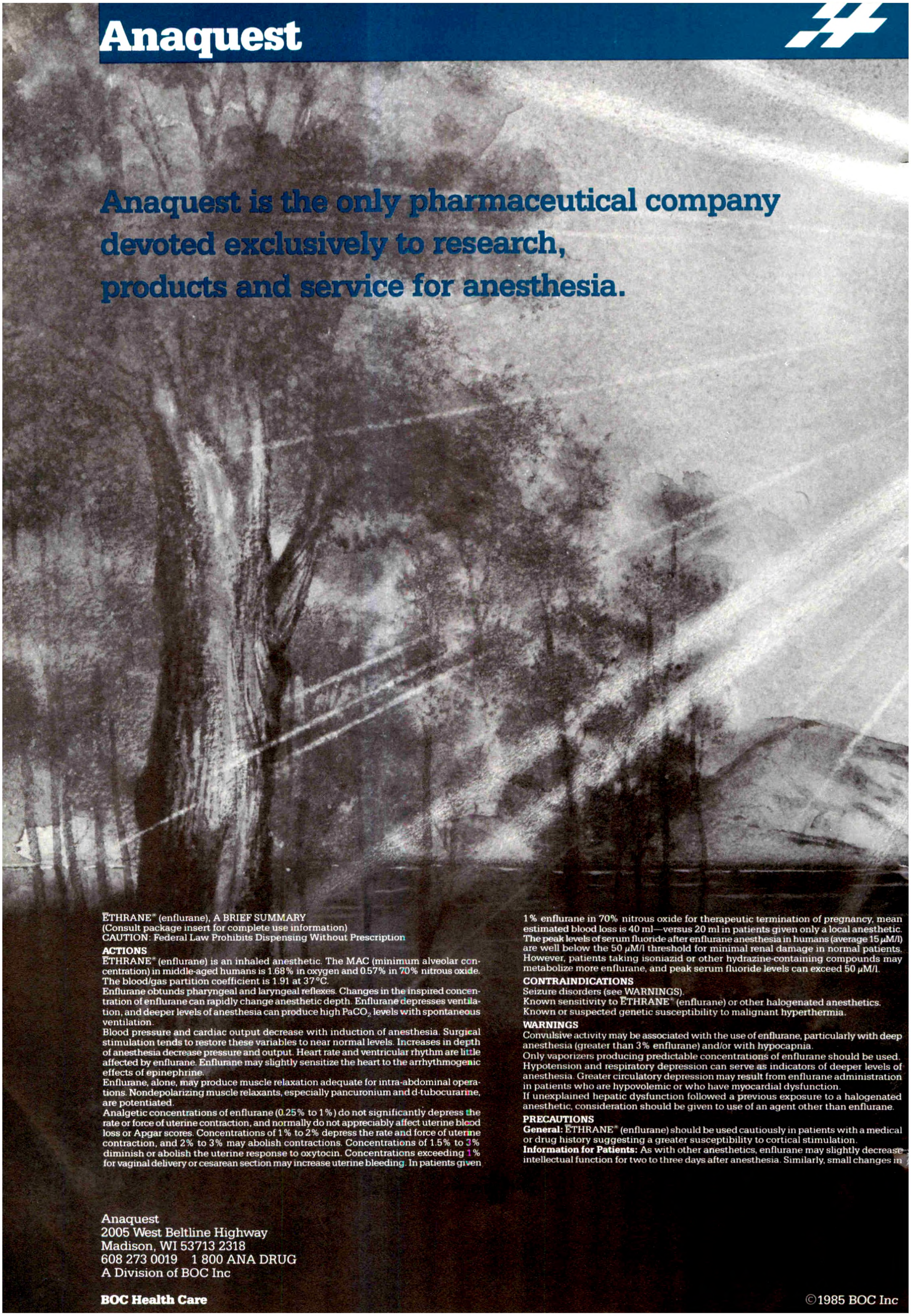
- ☐ The full term for which an abbreviation stands should precede its first use in the text unless it is a standard unit of measurement. Avoid abbreviations in the title.
- ☐ Do not synthesize new or unusual abbreviations. When many abbreviations are used, include all in a box of definitions at the start of the article.
- ☐ Consult the following sources for abbreviations:
  1. CBE Style Manual Committee. Council of Biology Editors style manual: a guide for authors, editors, and publishers in the biological sciences. 4th ed. Arlington, Virginia: Council of Biology Editors, 1978; and
  2. O'Connor M, Woodford FP. Writing scientific papers in English: an ELSE-Ciba Foundation guide for authors. Amsterdam: Elsevier-Excerpta Medica, 1975.

## Ethical Principles

- ☐ When reporting experiments on human subjects, indicate whether the procedures followed were in accord with the ethical standards of the Committee on Human Experimentation of the institution in which the experiments were done or are in accord with the Helsinki Declaration of 1975.
- ☐ When reporting experiments on animal subjects, indicate whether the institution's or the National Research Council's guide for the care and use of laboratory animals was followed.

## Exclusive Publication Statement

- ☐ The principal author of all materials submitted for publication (except letters to the editor) must include in a covering letter a statement to the effect that none of the material in this manuscript has been published previously nor is any of this material currently under consideration for publication elsewhere.
- ☐ Authors will be asked to transfer copyright of articles accepted for publication to the International Anesthesia Research Society.


Anaquest
Anaquest is the only pharmaceutical company devoted exclusively to research, products and service for anesthesia.

ĒTHRANE® (enflurane), A BRIEF SUMMARY
(Consult package insert for complete use information)
CAUTION: Federal Law Prohibits Dispensing Without Prescription

**ACTIONS**

ĒTHRANE® (enflurane) is an inhaled anesthetic. The MAC (minimum alveolar concentration) in middle-aged humans is 1.68% in oxygen and 0.57% in 70% nitrous oxide. The blood/gas partition coefficient is 1.91 at 37 °C.

Enflurane obtunds pharyngeal and laryngeal reflexes. Changes in the inspired concentration of enflurane can rapidly change anesthetic depth. Enflurane depresses ventilation, and deeper levels of anesthesia can produce high $PaCO_2$ levels with spontaneous ventilation.

Blood pressure and cardiac output decrease with induction of anesthesia. Surgical stimulation tends to restore these variables to near normal levels. Increases in depth of anesthesia decrease pressure and output. Heart rate and ventricular rhythm are little affected by enflurane. Enflurane may slightly sensitize the heart to the arrhythmogenic effects of epinephrine.

Enflurane, alone, may produce muscle relaxation adequate for intra-abdominal operations. Nondepolarizing muscle relaxants, especially pancuronium and d-tubocurarine, are potentiated.

Analgetic concentrations of enflurane (0.25% to 1%) do not significantly depress the rate or force of uterine contraction, and normally do not appreciably affect uterine blood loss or Apgar scores. Concentrations of 1% to 2% depress the rate and force of uterine contraction, and 2% to 3% may abolish contractions. Concentrations of 1.5% to 3% diminish or abolish the uterine response to oxytocin. Concentrations exceeding 1% for vaginal delivery or cesarean section may increase uterine bleeding. In patients given 1% enflurane in 70% nitrous oxide for therapeutic termination of pregnancy, mean estimated blood loss is 40 ml—versus 20 ml in patients given only a local anesthetic.

The peak levels of serum fluoride after enflurane anesthesia in humans (average 15 μM/l) are well below the 50 μM/l threshold for minimal renal damage in normal patients. However, patients taking isoniazid or other hydrazine-containing compounds may metabolize more enflurane, and peak serum fluoride levels can exceed 50 μM/l.

**CONTRAINDICATIONS**

Seizure disorders (see WARNINGS).
Known sensitivity to ĒTHRANE® (enflurane) or other halogenated anesthetics.
Known or suspected genetic susceptibility to malignant hyperthermia.

**WARNINGS**

Convulsive activity may be associated with the use of enflurane, particularly with deep anesthesia (greater than 3% enflurane) and/or with hypocapnia.

Only vaporizers producing predictable concentrations of enflurane should be used.

Hypotension and respiratory depression can serve as indicators of deeper levels of anesthesia. Greater circulatory depression may result from enflurane administration in patients who are hypovolemic or who have myocardial dysfunction.

If unexplained hepatic dysfunction followed a previous exposure to a halogenated anesthetic, consideration should be given to use of an agent other than enflurane.

**PRECAUTIONS**

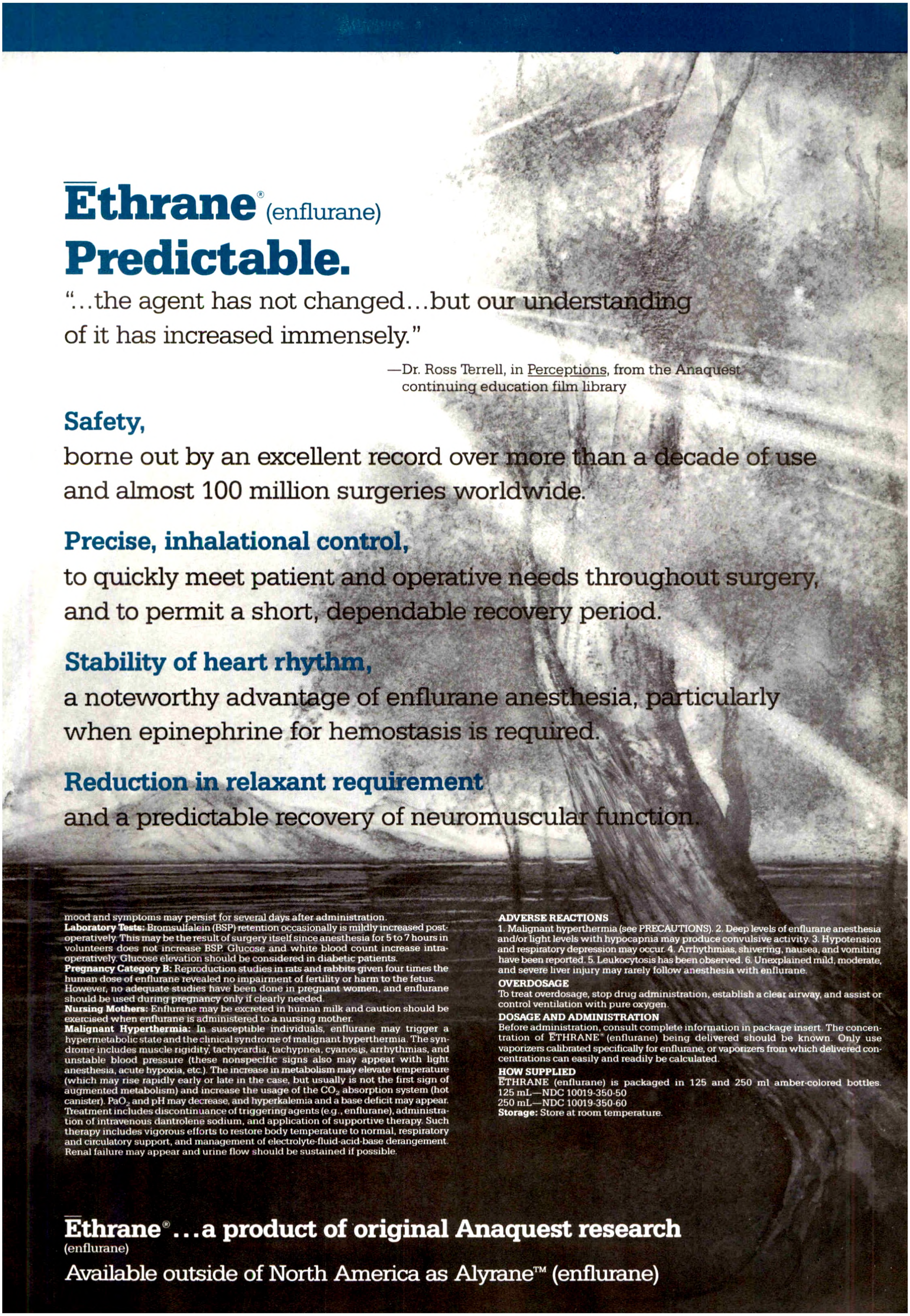
**General:** ĒTHRANE® (enflurane) should be used cautiously in patients with a medical or drug history suggesting a greater susceptibility to cortical stimulation.

**Information for Patients:** As with other anesthetics, enflurane may slightly decrease intellectual function for two to three days after anesthesia. Similarly, small changes in

Anaquest
2005 West Beltline Highway
Madison, WI 53713 2318
608 273 0019    1 800 ANA DRUG
A Division of BOC Inc

**BOC Health Care**

©1985 BOC Inc



# Ethrane® (enflurane)

# Predictable.

"...the agent has not changed...but our understanding of it has increased immensely."

—Dr. Ross Terrell, in Perceptions, from the Anaquest continuing education film library

## Safety,

borne out by an excellent record over more than a decade of use and almost 100 million surgeries worldwide.

## Precise, inhalational control,

to quickly meet patient and operative needs throughout surgery, and to permit a short, dependable recovery period.

## Stability of heart rhythm,

a noteworthy advantage of enflurane anesthesia, particularly when epinephrine for hemostasis is required.

## Reduction in relaxant requirement

and a predictable recovery of neuromuscular function.

mood and symptoms may persist for several days after administration.

**Laboratory Tests:** Bromsulfalein (BSP) retention occasionally is mildly increased postoperatively. This may be the result of surgery itself since anesthesia for 5 to 7 hours in volunteers does not increase BSP. Glucose and white blood count increase intraoperatively. Glucose elevation should be considered in diabetic patients.

**Pregnancy Category B:** Reproduction studies in rats and rabbits given four times the human dose of enflurane revealed no impairment of fertility or harm to the fetus. However, no adequate studies have been done in pregnant women, and enflurane should be used during pregnancy only if clearly needed.

**Nursing Mothers:** Enflurane may be excreted in human milk and caution should be exercised when enflurane is administered to a nursing mother.

**Malignant Hyperthermia:** In susceptible individuals, enflurane may trigger a hypermetabolic state and the clinical syndrome of malignant hyperthermia. The syndrome includes muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure (these nonspecific signs also may appear with light anesthesia, acute hypoxia, etc.). The increase in metabolism may elevate temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and increase the usage of the $CO_2$ absorption system (hot canister). $PaO_2$ and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., enflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support, and management of electrolyte-fluid-acid-base derangement. Renal failure may appear and urine flow should be sustained if possible.

### ADVERSE REACTIONS

1. Malignant hyperthermia (see PRECAUTIONS). 2. Deep levels of enflurane anesthesia and/or light levels with hypocapnia may produce convulsive activity. 3. Hypotension and respiratory depression may occur. 4. Arrhythmias, shivering, nausea, and vomiting have been reported. 5. Leukocytosis has been observed. 6. Unexplained mild, moderate, and severe liver injury may rarely follow anesthesia with enflurane.

### OVERDOSAGE

To treat overdosage, stop drug administration, establish a clear airway, and assist or control ventilation with pure oxygen.

### DOSAGE AND ADMINISTRATION

Before administration, consult complete information in package insert. The concentration of ETHRANE® (enflurane) being delivered should be known. Only use vaporizers calibrated specifically for enflurane, or vaporizers from which delivered concentrations can easily and readily be calculated.

### HOW SUPPLIED

ETHRANE (enflurane) is packaged in 125 and 250 ml amber-colored bottles.
125 mL—NDC 10019-350-50
250 mL—NDC 10019-350-60

**Storage:** Store at room temperature.

**Ethrane®...a product of original Anaquest research**
(enflurane)

Available outside of North America as Alyrane™ (enflurane)

# Albumin & PPF are no safer or more effective than Hespan®

(hetastarch)

*...they're simply*

©1985 American Critical Care

## As safe as albumin or PPF

In comparative clinical studies, platelet counts, hematocrits, serum fibrinogen levels, prothrombin times (PT), and partial thromboplastin times (PTT) seen with Hespan were comparable to those seen with albumin or plasma protein fraction (PPF).[1,2]

Other studies demonstrate that when any reduction in platelet count or prolongation of PT or PTT does occur with Hespan, no increased bleeding results, even in patients with multiple trauma.[3-5] As with any volume expander, patients should be monitored for excessive hemodilution of coagulant factors or circulatory overload when large volumes are administered.

When Hespan-treated patients were monitored to detect localized or systemic sepsis, there was no evidence of a decrease in their ability to ward off infection or combat an established infection.[5]

Hespan is nonantigenic and, as with blood-derived colloids, any risk of allergic reaction is minimal. Hespan also has a negligible effect on subsequent blood typing or crossmatching.[6]

## As effective as albumin or PPF

Comparative clinical studies have repeatedly demonstrated that Hespan is as effective as albumin or PPF in postoperative myocardial revascularization,[1-3] and hemorrhagic, traumatic, or septic shock.[4,5,7]

No significant differences between Hespan and albumin or PPF were noted in any efficacy parameter.[1-5,7] Hespan effectively maintained colloid osmotic pressure, restored plasma volume, and improved cardiac output and renal function in hypovolemic patients.[1-5,7] And, the volume-expanding effect of a single infusion of Hespan can persist for 24 hours or longer.

## Half the price of albumin or PPF

Hespan offers a potential savings to your hospital of tens of thousands of dollars a year.

double the price.

For additional information, contact the Medical Services Department, American Critical Care, 1600 Waukegan Road, McGaw Park, IL 60085. Phone 1-800-323-4980.

**Lifesaving, moneysaving**

**HESPAN®**
(hetastarch)

**American Critical Care**

American Hospital Supply Corporation

*Please see references and brief summary of prescribing information on following page.*

**References:** 1. Diehl JT, Lester JL, Cosgrove DM: Clinical comparison of hetastarch and albumin in postoperative cardiac patients. *Ann Thorac Surg 34* (6):674-679, 1982. **2.** Moggio RA, Rha CC, Somberg ED, et al: Hemodynamic comparison of albumin and hydroxyethyl starch in postoperative cardiac surgery patients. *Crit Care Med 11* (12):943-945, 1983. **3.** Kirklin JK, Lell WA, Kouchoukos NT: Hydroxyethyl starch versus albumin for colloid infusion following cardiopulmonary bypass in patients undergoing myocardial revascularization. *Ann Thorac Surg 37* (1):40-46, 1984. **4.** Puri VK, Paidipaty B, White L: Hydroxyethyl starch for resuscitation of patients with hypovolemia and shock. *Crit Care Med 9* (12):833-837, 1981. **5.** Shatney CH, Deepika K, Militello PR, et al: Efficacy of hetastarch in the resuscitation of patients with multisystem trauma and shock. *Arch Surg 118*:804-809, 1983. **6.** Daniels MJ, Strauss RG, Smith-Floss AM: Effects of hydroxyethyl starch on erythrocyte typing and blood crossmatching. *Transfusion 22* (3):226-228, 1982. **7.** Rackow EC, Falk JL, Fein IA, et al: Fluid resuscitation in circulatory shock: A comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. *Crit Care Med 11*(11):839-850, 1983.

**HESPAN®** (hetastarch)

**6% Hetastarch in 0.9% Sodium Chloride Injection**

***CONTRAINDICATIONS***

Hetastarch is contraindicated in patients with severe bleeding disorders or with severe congestive cardiac and renal failure with oliguria or anuria.

***WARNINGS***

Large volumes may alter the coagulation mechanism. Thus, administration of hetastarch may result in transient prolongation of prothrombin, partial thromboplastin and clotting times. With administration of large doses, the physician should also be alert to the possibility of transient prolongation of bleeding time.

Hematocrit may be decreased and plasma proteins diluted excessively by administration of large volumes of hetastarch.

***Usage in Leukapheresis:*** Significant declines in platelet counts and hemoglobin levels have been observed in donors undergoing repeated leukapheresis procedures due to the volume expanding effects of hetastarch. Hemoglobin levels usually return to normal within 24 hours. Hemodilution by hetastarch and saline may also result in 24 hour declines of total protein, albumin, calcium and fibrinogen values.

***Usage in Pregnancy:*** Reproduction studies have been done in mice with no evidence of fetal damage. Relevance to humans is not known since hetastarch has not been given to pregnant women. Therefore, it should not be used in pregnant women, particularly during early pregnancy, unless in the judgment of the physician the potential benefits outweigh the potential hazards.

***Usage in Children:*** No data available pertaining to use in children.

The safety and compatibility of additives have not been established.

***PRECAUTIONS***

The possibility of circulatory overload should be kept in mind. Special care should be exercised in patients who have impaired renal clearance since this is the principal way in which hetastarch is eliminated. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Indirect bilirubin levels of 0.83 mg% (normal 0.0-0.7 mg%) have been reported in 2 out of 20 normal subjects who received multiple hetastarch infusions. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering hetastarch to patients with a history of liver disease.

Regular and frequent clinical evaluation and laboratory determinations are necessary for proper monitoring of hetastarch use during leukapheresis. Studies should include CBC, total leukocyte and platelet counts, leukocyte differential count, hemoglobin, hematocrit, prothrombin time (PT), and partial thromboplastin time (PTT).

Hetastarch is nonantigenic. However, allergic or sensitivity reactions have been reported (see ADVERSE REACTIONS). If such reactions occur, they are readily controlled by discontinuation of the drug and, if necessary, administration of an antihistaminic agent.

***ADVERSE REACTIONS***

The following have been reported: vomiting, mild temperature elevation, chills, itching, submaxillary and parotid glandular enlargement, mild influenza-like symptoms, headaches, muscle pains, peripheral edema of the lower extremities, and anaphylactoid reactions consisting of periorbital edema, urticaria, and wheezing.

***HOW SUPPLIED***

NDC **0094-0037-05-Hespan*** (6% Hetastarch in 0.9% Sodium Chloride Injection) is supplied sterile and nonpyrogenic in 500 ml intravenous infusion bottles.

***CAUTION***

Federal (U.S.A.) law prohibits dispensing without prescription.

Rev: Feb., 1982

Distributed by

**American Critical Care**

American Hospital Supply Corporation
McGaw Park, IL USA 60085

# IARS REVIEW COURSE LECTURES AVAILABLE

____ 1985, 59th Congress—26 Review Course Lectures—$6.00

____ 1984, 58th Congress—24 Review Course Lectures—$6.00

____ 1983, 57th Congress—16 Review Course Lectures—$5.00

____ 1982, 56th Congress—14 Review Course Lectures—$5.00

To:
International Anesthesia Research Society
3645 Warrensville Center Road
Cleveland, Ohio 44122

Please send Lecture Booklets checked above.

My check, payable to IARS in the amount of $__________ is enclosed.

______________________________
(Name)

______________________________
(Mail Address)

______________________________

______________________________
(City, State, Zip)

# DON'T SIGN ON THE DOTTED LINE...

## UNTIL YOU SEE THE NEW ADVANTAGE™ 2000 FROM PERKIN-ELMER!

If you're considering an anesthesia/respiratory monitoring system... Stop.

Get a hands-on look at this major breakthrough... the only system that gives you continuous patient monitoring along with the advantages of shared mass spectrometry.

See it at the American Society of Anesthesiology Meeting in San Francisco, October 14-16, Booth 1311.

**PERKIN-ELMER**

Perkin-Elmer Medical Instruments
2771 N. Garey Ave.
Pomona, CA 91767
(714) 593-3581, TWX 910-581-3826

# INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

## THE B.B. SANKEY IARS ANESTHESIA ADVANCEMENT AWARD

The B.B. Sankey Anesthesia Advancement Award has been established to expand upon and replace the IARS Research Award. This new award is intended to foster investigative efforts in the fields of anesthesia research, clinical care, education and administration.

The recipients of the 1985 Sankey Anesthesia Advancement Awards are:

Roger S. Brett, MD, PhD, State University of New York, Stony Brook, New York
Patrick Curling, MD, Emory University School of Medicine, Atlanta, Georgia
Richard F. Davis, MD, University of Florida College of Medicine, Gainesville, Florida

## 1986 B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

Applications for up to $25,000 are invited for the 1986 Award, subject to the following basic conditions:

- The proposal must be within the general field of anesthesiology and may be for research, clinical care, education or administration.
- The applicant must be a member of the International Anesthesia Research Society.
- Applications must be received in the IARS Cleveland office not later than December 16, 1985.
- The official application form for the award must be used. This form, as well as the guidelines for applicants, is available on request to:

Emerson A. Moffitt, MD
Executive Secretary
International Anesthesia Research Society
3645 Warrensville Center Road
Cleveland, Ohio 44122, USA
Telephone: (216) 295-1124

The 1986 Award(s) will be announced at the Annual Meeting (60th Congress) of the International Anesthesia Research Society to be held at Caesars Palace, Las Vegas, Nevada, March 15–19, 1986.

## Now Published by Elsevier

# Journal of the American Geriatrics Society

GENE H. STOLLERMAN, MD, *Editor, Boston University Hospitals, Boston, MA*
JOHN P. BLASS, MD, PhD, *Associate Editor, White Plains, NY*

***Section Editors***

HARVEY J. COHEN, MD
*Geriatric Bioscience*
*Durham, NC*

DAVID C. THOMASMA, PhD
*Medical Ethics and Humanities*
*Maywood, IL*

JOHN R. BALL, MD, JD
*Law and Public Policy*
*Washington, DC*

URIEL S. BARZEL, MD
*Book Reviews*
*Bronx, NY*

PATRICK W. IRVINE, MD
*Abstracts*
*St. Paul, MN*

***Editorial Board***
***Through 1985***

ROBERT BERKOW, MD
*Lansdale, PA*
*Psychosomatic Medicine*

GEORGE E. BURCH, MD
*New Orleans, LA*
*Cardiology*

EWALD W. BUSSE, MD
*Durham, NC*
*Bio-behavioral Sciences*

LEO M. COONEY, Jr., MD
*New Haven, CT*
*Rheumatology and Rehabilitation*

WILLIAM R. HAZZARD, MD
*Baltimore, MD*
*Metabolism and Endocrinology*

PETER P. LAMY, PhD, FCP
*Baltimore, MD*
*Pharmacotherapy*

JAY P SANFORD, MD
*Bethesda, MD*
*Infectious Diseases*

IRVING S. WRIGHT, MD
*New York, NY*
*Cardiovascular Disease*

***Through 1986***

DARRELL R. ABERNETHY, MD
*Houston, TX*
*Clinical Pharmacology*

DANIEL BLAZER, MD
*Durham, NC*
*Psychiatry and Epidemiology*

CLAIR COX, MD
*Memphis, TN*
*Urology*

EDMUND PELLEGRINO, MD
*Washington, DC*
*Philosophy and Ethics of Medicine*

NICHOLAS J. PISACANO, MD
*Lexington, KY*
*Family Medicine*

JOHN ROWE, MD
*Boston, MA*
*Gerontologic Physiology*

DAVID SOLOMON, MD
*Los Angeles, CA*
*Endocrinology*

SHELDON TOBIN, PhD
*Albany, NY*
*Health Psychology*

***Through 1987***

EVAN CALKINS, MD
*Buffalo, NY*
*Geriatric Medicine*

EDWARD D. FROHLICH, MD
*New Orleans, LA*
*Hypertension and Clinical Pharmacology*

JOHN E. MORLEY, MD
*Sepulveda, CA*
*Neuroendocrinology*

ARTHUR J. MOSS, MD
*Rochester, NY*
*Cardiovascular Diseases*

LAURENCE Z. RUBENSTEIN, MD, MPH
*Sepulveda, CA*
*Geriatric Health Services*

ROBERT D. TERRY, MD
*La Jolla, CA*
*Neuropathology*

STANLEY F. WAINAPEL, MD
*Boston, MA*
*Rehabilitation Medicine*

CHARLES E. WELLS, MD
*Nashville, TN*
*Psychiatry*

**Journal of the American Geriatrics Society** has been providing the medical community with outstanding original coverage of all aspects of geriatrics for over 30 years. Emphasizing original research, **Journal of the American Geriatrics Society** publishes both clinical and basic science studies on a broad range of topics. A distinguished editorial board, drawn from many medical specialties, ensures that the journal includes contributions from all areas of this interdisciplinary field.

Regular features of **Journal of the American Geriatrics Society** include:

- **Medical Ethics and Humanities**
  thought-provoking viewpoints on the difficult ethical questions facing all physicians who treat the elderly
- **Law and Public Policy**
  clear, concise reports on the latest legislative and judicial developments that affect patient management
- **Clinical Experience**
  practical solutions to common problems in geriatric health care delivery

Geriatricians, internists, cardiologists, rheumatologists, psychiatrists, endocrinologists, family practitioners, and others who treat older patients rely on **Journal of the American Geriatrics Society** for up-to-date information on all aspects of geriatric health care.

**Journal of the American Geriatrics Society** is abstracted/indexed in *Index Medicus, Current Contents, Science Citation Index, Automatic Subject Citation Alert, Social Sciences Citation Index,* and *ISI/Biomed.*

**1985 Subscription Information:**
**Journal of the American Geriatrics Society**
Volume 33, 12 issues, 1985
Personal Rate: **$50.00**
Institutional Rate: **$55.00**
Subscribers outside the U.S. and U.S. possessions should add **$15.00** for surface delivery or **$30.00** for air mail delivery. **Sample copies are available.**

**Elsevier**

## ORDER FORM

**Journal of the American Geriatrics Society**
Volume 33, 12 issues, ISSN 0002-8614, 1985

______ Please enter my subscription at the Institutional Rate of $55.00
______ Please enter my subscription at the Personal Rate of $50.00
______ Please send me a free sample copy.

Subscribers outside the U.S. and U.S. possessions should add **$15.00** for surface delivery or **$30.00** for air mail delivery.

**Payment**
**Enclosed please find my:** ☐ personal check ☐ bank draft
☐ UNESCO coupons in the amount of ______
**Please charge to:** ☐ American Express ☐ VISA
☐ MasterCard/Access/Eurocard (issuing bank # ______)

Account # ______ Expires ______

Signature ______

☐ **Please bill me.** (Orders from non-U.S. customers must be prepaid.)

Name ______

Institution ______

Address ______

City ______

State ______ Zip/Postal Code ______

For sample copies, send to

**in North and South America:**
Elsevier Science Publishing Co., Inc.
P.O. Box 1663, Grand Central Station, New York, NY 10163

**in the rest of the world:**
Elsevier Science Publishers, Direct Mail Department
P.O. Box 211, 1000 AE Amsterdam, The Netherlands

**Note: Send subscription orders to either your usual supplier or the New York address.** All subscriptions begin with the first issue of the calendar year. Subscription rates valid through Dec. 31, 1985. 7/85 EB329

**JEFFERSON MEDICAL COLLEGE**
**THOMAS JEFFERSON UNIVERSITY**
***IN HISTORIC PHILADELPHIA***

**THE DEPARTMENT OF OTOLARYNGOLOGY AND THE OFFICE OF CONTINUING MEDICAL EDUCATION**

present

## THE USE OF THE $CO_2$ LASER FOR HEAD AND NECK SURGERY

at Jefferson Medical College
Philadelphia, PA.

A two day workshop given on the following dates:
September 27-28, 1985
December 6-7, 1985
February 21-22, 1986
April 18-19, 1986

**ANESTHESIOLOGISTS:**
- limited to 28 participants
- **8 credit hours** in Category I
- participation in Day I of each two day workshop
- fee: **$300.00**

**OTOLARYNGOLOGISTS:**
- limited to 12 participants
- **16 credit hours** in Category I
- participation in Day I and Day II, including four (4) hours of laboratory exercises.
- fee: **$850.00**

Registration fee includes course syllabus, continental breakfasts, coffee breaks, luncheons and an evening banquet.

For information regarding registration call:
**Office of Continuing Medical Education**
**(215) 928-6992**

For information regarding course content call:
**LOUIS D. LOWRY, M.D., PROGRAM DIRECTOR**
**STEVEN R. CHESNICK, M.D., CO-DIRECTOR**
**AT (215) 928-6784**

*tear out and mail to:*
**THE USE OF THE $CO_2$ LASER**
**FOR HEAD AND NECK SURGERY**
**Jefferson Medical College**
**Office of Continuing Medical Education**
**1025 Walnut Street • Philadelphia, PA. 19107**

Name____________________
Address____________________
City____________________
State__________ Zip Code__________
Date of workshop you wish to attend__________
Phone____________________

---

## 10th CARIBBEAN SYMPOSIUM IN ANESTHESIOLOGY AND RELATED FIELDS

**DECEMBER 4–8, 1985**
**CARIBE HILTON HOTEL**
**SAN JUAN, PUERTO RICO**

***"THE SUBSPECIALTIES OF ANESTHESIOLOGY"***

For information write:

Miguel Colón-Morales, M.D.
G.P.O. Box 4547
San Juan, Puerto Rico 00936
(809) 758-9200

---

## 24th CLINICAL CONFERENCE IN PEDIATRIC ANESTHESIOLOGY

**JANUARY 24, 25, & 26, 1986**

To Be Held At The:

Los Angeles Marriott Hotel

For Information Write To:

**Wayne Herbert, M.D.**
**Program Director**
**Pediatric Anesthesiology Foundation**
**Childrens Hospital of Los Angeles**
**P.O. Box 54700**
**Los Angeles, CA 90054**

# Classified Advertising

**PERMANENT POSITION WANTED**
CRNA—experienced, wishes busy situation, solo or group, best of remuneration. 1-800-521-6750.

**EAST CENTRAL ILLINOIS**
Progressive 210 bed hospital seeking boarded Anesthesiologists. Attractive college town. Average 400 surgeries monthly. Send CV to Bill Rauwolf, SBLHC, Box 372, Mattoon, IL 61938.

**FREELANCE ANESTHETISTS**
Temporary & Permanent—Medical Anesthesiologists—CRNAs/Home based throughout US. If you need an anesthetist call 800-521-6750, ALL-STATES MEDICAL PLACEMENT AGENCY, Box 91, LaSalle, MI 48145 or 313-241-1418 (MI).

**TRANS-AMERICAN ANESTHETISTS, WEST**
Temporary or Permanent MDAs, CRNAs, ready to serve you, up-to-date skills, cooperative, licensed, insured professionals caring about you. Call 800-762-1258, Box 24432, Colorado Springs, CO 80918, or 303/598-2788 (CO).

**ANESTHESIOLOGISTS**
Excellent, prequalified individuals available to join your group on a career or temporary basis. For more information please contact: Southwest Anesthesia Services, PO Box 5719, Santa Fe, New Mexico 87502, (505) 983-7371.

**THE ELLIS FISCHEL STATE CANCER CENTER**
is searching for a Director of Anesthesiology. The director would be expected to provide general and regional anesthesia for all types of cancer surgery. Teaching opportunities are available. Salary is competitive. Contact William G. Kraybill, MD, Chairman of Search Committee for Anesthesiology, Ellis Fischel State Cancer Center, Columbia, MO 65201, or phone 314-875-2214. An equal opportunity employer.

**ROCKY MTS./SOUTHWEST**
We have career and temporary positions available from solo to large group practice in the Rocky Mts. and Southwest. Expenses paid; partnerships usually available. Please contact Southwest Anesthesia Services, R.R. #9 Box 96 MM, Santa Fe, NM 87501. (505) 983-7371.

**LOUISIANA—BOARD CERTIFIED ANESTHESIOLOGISTS**
Louisiana State University School of Medicine in Shreveport has immediate openings for faculty personnel in the Department of Anesthesiology. Academic rank commensurate with education and experience. Excellent financial and fringe benefits offered at all ranks. Shreveport, with a metropolitan area population of 350,000, has a progressive, growing and expanding medical school with an extremely challenging high-risk patient population. An active transplant service is also in operation. Please send curriculum vitae and immediate reply to Norman H. Blass, MD, Professor and Chairman, Department of Anesthesiology, Louisiana State University School of Medicine, 1501 Kings Highway, Shreveport, LA 71130-3932. An affirmative action/equal opportunity employer.

**LOYOLA UNIVERSITY STRITCH SCHOOL OF MEDICINE,**
Maywood, Illinois, located 10 miles from downtown Chicago in the western suburbs. The Department of Anesthesiology is seeking two faculty at the level of assistant or associate professor, depending on experience and academic achievement. Candidates must be board certified with clinical and academic experience and interest in teaching. One position is for a cardiovascular anesthesiologist with experience in invasive monitoring. The second position is for a pediatric anesthesiologist with either board certification in pediatrics or fellowship, and at least 1–2 years of experience in pediatric anesthesia. Faculty rank, salary, and benefits are commensurate with experience. Send curriculum vitae to T.L.K. Rao, MD, Chairman, Department of Anesthesiology, Loyola University, 2160 S. First Avenue, Maywood, IL 60153.

**TUTORING FOR WRITTEN AND ORAL BOARD EXAMS**
Individual or small group sessions given in New York City, San Francisco, and Hawaii. Basic science emphasis. Call 415-321-1117, or reply to Box 1116, Menlo Park, CA 94026.

**CHAIRPERSON—DEPARTMENT OF ANESTHESIOLOGY**
The University of Nebraska College of Medicine is conducting an active search for a Chairperson of Anesthesiology. Applications are sought from board certified individuals with established credentials in research and demonstrated leadership in education. Interested applicants should submit a curriculum vitae by October 15, 1985, to Leon F. Davis, DDS, MD, Office of the Dean, University of Nebraska College of Medicine, 42nd Street and Dewey Avenue, Omaha, Nebraska 68105. The University of Nebraska is an affirmative action/equal opportunity employer.

**NEW ENGLAND SEA COAST**
Group of anesthesiologists in medium-sized community hospital seek partner. Must be B/C (or B/E with fellowship). All surgeries except cardiac. Sea coast area of New England; easy access to recreational and cultural activities. Reply with CV to Box G16, % *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

**ANESTHESIOLOGIST NEEDED**
BE/BC. Young staff, progressive hospital on beautiful shores of Western Michigan. All types of surgery except open-heart, no OB. Experience in pain management required. Salary negotiable. Send CV to M.J. Kilbride, DO, Muskegon General Hospital, 1700 Oak Avenue, Muskegon, MI 49442.

**UTAH**
The University of Utah seeks an anesthesiologist who is board certified in anesthesiology, preferably with a PhD in physiology or pharmacology for a position at the level of Assistant Professor. Candidates should be qualified in clinical care, have previous teaching experience, and be capable of independent basic science research. Send curriculum vitae to K.C. Wong, MD, Chairman,

**CLASSIFIED ADS**

*Anesthesia and Analgesia* makes available classified advertising space for those interested in obtaining positions, or wishing to announce meetings, postgraduate courses, or other events. Display space (minimum ¼ page) is also available through Pharmaceutical Media, Inc. Rates for classified advertising: $.90 per word, minimum twenty words; box number ads $1.00 per word. Copy deadline 7 weeks prior to publication, e.g., for the March issue, copy should be received by the 1st of January. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. Ad copy, subject to acceptance by publisher, should be mailed to:

*Anesthesia and Analgesia*
Desk Editorial
Classified Ads
Elsevier Science Publishing Co, Inc,
52 Vanderbilt Avenue, New York, NY 10017.
Make checks payable to Elsevier Science Publishing Co, Inc.

Department of Anesthesiology, University of Utah, College of Medicine, 50 North Medical Drive, Salt Lake City, Utah 84132. Equal opportunity/affirmative action employer.

---

### UTAH

The University of Utah seeks an anesthesiologist who is board certified/eligible in anesthesiology and who has completed a formal fellowship in pain. Opportunity to do clinical anesthesia, pain management, and research. Competitive academic salaries at the Instructor level. Send curriculum vitae to K.C. Wong, MD, Chairman, Department of Anesthesiology, University of Utah, College of Medicine, 50 North Medical Drive, Salt Lake City, UT 84132. Equal opportunity/affirmative action employer.

---

### POSITION NOW AVAILABLE

for board certified/eligible anesthesiologist to join three-member incorporated group with CRNAs in a very progressive community hospital. All types of procedures except open heart. Send CV to Box F23, ℅ *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

---

### PRIVATE TUTORING AVAILABLE FOR WRITTEN AND ORAL BOARD EXAMS

Send name, address, and phone to Box ANA 5-84-E, ℅ *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Co., Inc., 52 Vanderbilt Avenue, New York, NY 10017.

---

### ANESTHESIOLOGIST

Board certified anesthesiologist, 3–5 years experience for busy mid-west practice in 700-bed hospital. Send CV to Box H19, ℅ *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

---

### WORLDWIDE ANESTHESIA

is an exciting organization of anesthesiologists and CRNAs who specialize in relief services and provide qualified candidates for permanent positions throughout the US. To be included in our computerized data base or to recruit from the nation's largest resources of anesthesia personnel, call or write Worldwide Anesthesia, Box 1547, Ukiah, CA 95482. Nationwide 1-800-327-8427. "Over a decade of placement experience."

---

### MISSOURI

200-bed university pediatric hospital; 200 CV anesthetics/yr. 5500 anesthetics/yr. Full-time university faculty position includes malpractice, life, disability, and health insurance and retirement fringe benefits. Minimum: one year fellowship in pediatric anesthesia. Send CV to John F. Schweiss, MD, Professor and Chairman, Department of Anesthesiology, St. Louis University School of Medicine, 1325 South Grand Boulevard, St. Louis, MO 63104.

---

### ANESTHESIOLOGIST

to join a group of anesthesiologists and anesthetists in a college town in the Northeast. One and one-half hours from a large city. No open heart or neurosurgery. Nearby skiing, hunting, and fishing. Immediate opening, but will wait for suitable candidate. Send CV and references to Box F20, ℅ *Anesthesia and Analgesia*, Desk Editorial, 52 Vanderbilt Avenue, New York, NY 10017.

---

### NEW YORK: PEDIATRIC ANESTHESIOLOGIST

Expanding Division of Pediatric Anesthesia, Department of Anesthesiology, Columbia University College of Physicians and Surgeons is seeking individuals with training in anesthesia and pediatrics. Division responsibilities are in the operating room and intensive care unit. Applicants should possess excellent clinical and teaching skills as well as research interests. Interested individuals should reply to **Peter Rothstein, MD, Director, Division of Pediatric Anesthesia, Box 62, Babies Hospital, 622 West 168th Street, New York, NY 10032.** Columbia University is an equal opportunity employer.

---

### BC UNIVERSITY-TRAINED AMG OBSTETRICAL ANESTHESIOLOGIST

Presently in academic position looking for private practice position in OB anesthesia in NYC metropolitan area. Please respond to Box H20, ℅ Desk Editorial, *Anesthesia and Analgesia*, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

---

### NORTH CAROLINA

Temporary and permanent BE/BC anesthesiologists needed to join fee-for-service group in small community in heart of Blue Ridge Mountains. Salary first year. Send inquiries and CV to Watauga Anesthesia Associates, PA, 301 Birch Street, Boone, NC 28607.

---

### BC ANESTHESIOLOGIST

American graduated and trained, 22 years experience in all types of anesthesia including OPD and administration. Seeking position in Ohio but will consider other states. Will work with CRNAs. Send replies to Box H21, ℅ Desk Editorial, *Anesthesia and Analgesia*, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

---

### THE DEPARTMENT OF ANESTHESIOLOGY, ORAL ROBERTS UNIVERSITY SCHOOL OF MEDICINE

currently has openings for Assistant/Associate Professor with interests in teaching, clinical practice and research. Excellent opportunity for board eligible/board certified physician in an institution dedicated to philosophy of Whole Person Medicine. Rank and salary commensurate with qualifications and negotiable. The City of Faith Medical and Research Center is a Christian ministry that employs without regard to race, color, sex, age, handicap, national origin or status as a veteran. Send CV and names of three references to James Mayhew, MD, Chairman, Department of Anesthesiology, Oral Roberts University School of Medicine, City of Faith Medical & Research Center, 8181 South Lewis, Tulsa, OK 74137-1270.

---

### TEXAS: PEDIATRIC ANESTHESIOLOGIST

Excellent opportunity available for BC/BE pediatric anesthesiologist with minimum one year pediatric fellowship. Be second person in exciting practice serving two children's hospitals. Experience in pediatric cardiology, PICU, NICU or pulmonology helpful. Hospitals offer all subspecialities. Must be eligible for Texas license (FLEX required). Benefits include competitive salary, malpractice, profit sharing leading to partnership. If living in a city filled with cultural, recreational, and academic facilities while practicing in two of the SW's finest hospitals appeals to you, submit a CV with three references to Search Director, PO Box 2138, Fort Worth, TX 76113.

---

### ANESTHESIOLOGY FELLOW

Two openings for 1-yr obstetrical anesthesia fellowship, one beginning January 1986 and the other, July 1986. Program includes 6 months each in the Departments of Anesthesiology at UCI Medical Center and Memorial Hospital Medical Center, Long Beach. Both are Level 3 Perinatal Centers with 4000 deliveries per year. there is opportunity to take part in clinical research and teaching of medical students. Applicants must be eligible for California state licensure. Inquiries from all qualified applicants are welcome. Contact Ho Joon Choi, MD, Director of Obstetric Anesthesia, University of California, Irvine Medical Center, 81A, Orange, CA 92668.

---

### ANESTHESIOLOGIST

Male, five years of practice, experience in all types and techniques of anesthesia with a strong surgical background. Seeking full-time position. All offers considered. Reply to Box J21, ℅ Desk Editorial, *Anesthesia and Analgesia*, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

## WEST VIRGINIA UNIVERSITY

Seeking neuroanesthesiologist, pediatric anesthesiologist, and obstetrical anesthesiologist. Academic rank commensurate with credentials. Competitive salary. Applicants must have four postdoctoral years of training, including Clinical Base, Clinical Anesthesia and a Specialized Year. Applicants must have interest in clinical and didactic teaching of residents and medical students. New Hospital under construction. Morgantown is an excellent outdoor recreational community. West Virginia University is an Affirmative Action/Equal Opportunity Employer.

Please reply with resume to:

**Richard W. Eller, M.D., Chairman**
**Department of Anesthesiology**
**WVU Medical Center**
**Morgantown, WV 26506**

---

## ANESTHESIOLOGISTS

**St. Vincent Medical Center's Anesthesia Department** is expanding. We are seeking 2 board certified or board eligible anesthesiologists to join an 8 member BC/BE group with 15 CRNA's.

You will need 3 to 5 years experience with all types of anesthesia and intra-monitoring techniques.

**St. Vincent** is a 741-bed community teaching hospital with full surgical facilities, including neurological, open heart, retinal, vascular, obstetrical, plastic, as well as ambulatory outpatient surgery.

Located in one of Ohio's newest cities, Toledo boasts of spectacular waterfront developments, an art museum, symphony, theater and zoo rated among the top ten in the country, fine restaurants and shopping centers. In addition, year-round sports facilities are available along with spectator sports such as baseball and hockey.

For immediate consideration, please send your C.V. and a cover letter to: **Lynn Scott, Manager Recruitment Employment,**

St. Vincent Medical Center
**2213 Cherry St. • Toledo, OH 43608**
An Equal Opportunity Employer

---

## CBE STYLE MANUAL
### Fifth Edition

**A guide for Authors, Editors, and Publishers in the Biological Sciences**

Widely accepted and recommended as the standard reference for journals and books in the biological sciences

Special features of this newly updated and greatly expanded edition include:

- four new chapters;
- reorganization of the "Manuscript Preparation" section for easier reference;
- new conventions in the chapter on "Style in Special Fields";
- complete revision of the section on "Plant Sciences";
- cross-listing of "Abbreviations and Symbols";

and much more . . .

*CONTENTS:* Ethical conduct in authorship and publication • Planning the communication • Writing the article • Prose style for scientific writing • References • Illustrative materials • Editorial review of manuscripts • Application of copyright law • Manuscript into print • Proof correction • Indexing • General style conventions • Style in special fields • Abbreviations and symbols • Word usage • Secondary services for literature searching • Useful references with annotations • Subject index

ISBN: 0-914340-04-2; clothbound; publication date: September 1983; trim size 6 x 9 inches; 324 pages

*Regular Price:* $24.00 (10% discount on 10 or more copies delivered to one address)
*CBE Member Price:* $21.50 (single copy paid by personal check)

*Terms of Sale:* All sales final; no returns.
Prepayment required; U.S. currency drawn on a U.S. bank.
Price includes BOOK RATE postage.
For faster delivery--first class, air mail, or UPS available at additional charge (book weight 1 lb 9 oz).
Maryland residents, please add 5% sales tax.

*Mail your order with payment to:*
COUNCIL OF BIOLOGY EDITORS, INC.
9650 Rockville Pike, Bethesda, MD 20814

---

## ANESTHESIA STAFFING CRISIS

CALL 1-800 FAST GAS (327-8427)
24 HOUR HOT LINE

WORLDWIDE ANESTHESIA ASSOCIATES, INC.

THE NATION'S LARGEST PROVIDER OF PROFESSIONAL ANESTHESIA PERSONNEL

ANESTHESIOLOGISTS • CERTIFIED REGISTERED NURSE ANESTHETISTS • EMERGENCY AND SCHEDULED RELIEF • LOCUM TENENS • CONTRACT MANAGEMENT • PERMANENT RECRUITING •

Worldwide Anesthesia Associates, Inc.

P.O. Box 1547 • UKIAH, CALIFORNIA 95482 • U.S.A.

# INDEX TO ADVERTISERS

- American Critical Care
  - *Hespan* A40 thru A42
- American Pharmaseal Co.
  - *CTL* Cover 3
- Anaquest
  - *Enlon* A14 thru A16
  - *Ethrane* A38, A39
- Breon Laboratories
  - *Marcaine* A33, A34
- Bristol Laboratories
  - *Stadol* Cover 4
- Burroughs Wellcome Co.
  - *Tracrium* A21 thru A24, A32
- Caribbean Symposia in Anesthesiology & Related Fields
  - *Continuing Education* A46
- Classified Advertising A47, A48
- Jefferson Medical College
  - *Continuing Education* A46
- McGill University
  - *Harold R. Griffith Chair* A12
- Novametrix Medical Systems, Inc.
  - *Capnogard* A11
  - *Institutional* A6, A7
  - *Pulse Oximeter* A9
  - *Transcutaneous Monitor* A13
- Ohmeda
  - *Biox Oximeter* A25
- Olympus Medical
  - *LF-1* A17, A18
- Organon Pharmaceuticals
  - *Norcuron* Cover 2, A1, A2
  - *Regonal* A30, A31
- Pediatric Anesthesiology Foundation
  - *Continuing Education* A46
- Perkin Elmer
  - *Monitoring System* A43
- ProTech Pacific
  - *ProPillow* A10
  - *Strapeze* A20
- Hoffman La Roche, Inc.
  - *Injectable Valium* A26 thru A28
- St. Vincent Medical Center
  - *Employment Opportunity* A49
- Siemens Corporation
  - *Servo Anesthesia System* A29
- West Virginia University
  - *Employment Opportunities* A49
- Worldwide Anesthesia Associates, Inc.
  - *Employment Opportunities* A49
- Yearbook Medical Publishers A12

# CHOICE

## Introducing the Pharmaseal® Custom Catheter Insertion Tray Program

No two patients, no two physicians, no two procedures are alike. Why should two trays be?

We understand your need for versatility of product selection, and in response, we've designed our new *Custom* Catheter Insertion Tray Program. Now, you have a choice.

You can create your own trays from our full line of components. And once we receive your order, we'll deliver your custom trays in just 45 days. That's uncustomarily fast.

Working closely with your Pharmaseal representative, you can design the ideal trays for your pulmonary artery and central vein catheterization procedures.

Choose from over 165 high quality components, including a wide range of catheters and catheter components. Select local anesthetic, prepping and guiding components, and much more.

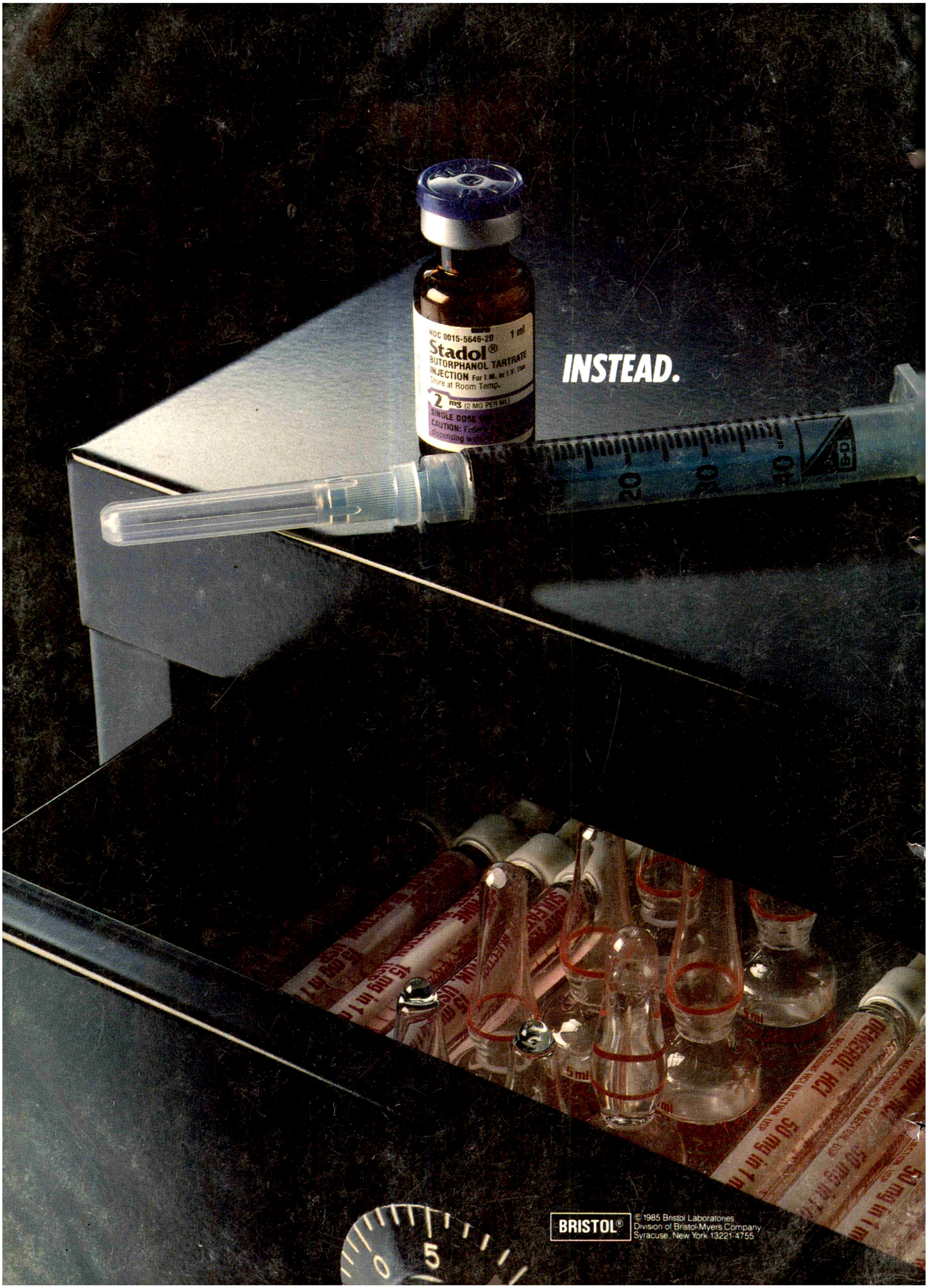
The Pharmaseal Custom Catheter Insertion Tray Program. Make it your first choice for all your needs.

For more information, contact American Pharmaseal Company, P.O. Box 5900, Valencia, CA 91355-8900. Or call toll-free 1-800-242-3549.

**American Pharmaseal Company**

American Hospital Supply Corporation

© American Hospital Supply Corporation



**BRISTOL®**

© 1985 Bristol Laboratories
Division of Bristol-Myers Company
Syracuse, New York 13221-4755

ISSN 0003-2999
Volume 64, Number 11, November 1985

Acc.
9.12.86

# Anesthesia and Analgesia

**Journal of the International Anesthesia Research Society**
Oldest Publication in the Specialty—Established 1922

Because the longer procedure raises the surgical risk...

**PAVULON®**

(pancuronium bromide injection)

Your best choice for 60-plus minutes of dependable relaxation... in every type of patient

Organon

**Organon Pharmaceuticals**
A Division of Organon Inc.
West Orange, N.J. 07052

Please see preceding page for brief summary of prescribing information.

**PAVULON***
(pancuronium bromide, injection)

**BRIEF SUMMARY**
**(Please consult package insert for full prescribing information.)**

THIS DRUG SHOULD ONLY BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS

**ACTIONS:** Pavulon is a non-depolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform) on the myoneural junction.

Pavulon (pancuronium bromide) is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, clindamycin, kanamycin, gentamicin and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

**CONTRAINDICATIONS:** Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion.

**WARNINGS:** PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS, WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

In patients who are known to have myasthenia gravis small doses of Pavulon may have profound effects. A peripheral nerve stimulator is especially valuable in assessing the effects of Pavulon in such patients.

**USAGE IN PREGNANCY:** The safe use of pancuronium bromide has not been established with respec to the possible adverse effects upon fetal development. Therefore, it should not be used in womei of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

Pavulon may be used in operative obstetrics (Cesarean section), but reversal of pancuronium may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy, becaus magnesium salts enhance neuromuscular blockade. Dosage should usually be reduced, as indicated, in such cases.

**PRECAUTIONS:** Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

**ADVERSE REACTIONS:** Neuromuscular: the most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonge skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: A slight increase in pulse rate is frequently noted.

Gastrointestinal: Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of Pavulon.

Respiratory: One case of wheezing, responding to deepening of the inhalational anesthetic, has been reported.

**DRUG INTERACTION:** The intensity of blockade and duration of action of Pavulon is increased in patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane.

Prior administration of succinylcholine, such as that used for endotracheal intubation, enhances the relaxant effect of Pavulon and the duration of action. If succinylcholine is used before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows signs of wearing off.

**DOSAGE AND ADMINISTRATION:** Pavulon should be administered only by or under the supervision of experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. See package insert for suggested dosages.

**CAUTION:** Federal law prohibits dispensing without prescription.

**HOW SUPPLIED:**
2 ml. ampuls–2 mg./ml.–boxes of 25, NDC #0052-0444-26
5 ml. ampuls–2 mg./ml.–boxes of 25, NDC #0052-0444-25
10 ml. vials–1 mg./ml.–boxes of 25, NDC #0052-0443-25

Organon

**Organon Pharmaceuticals**
A Division of Organon Inc.
West Orange, N.J. 07052

# IARS REVIEW COURSE LECTURES AVAILABLE

____ 1984, 58th Congress—24 Review Course Lectures—$6.00

____ 1983, 57th Congress—16 Review Course Lectures—$5.00

____ 1982, 56th Congress—14 Review Course Lectures—$5.00

To:
International Anesthesia Research Society
3645 Warrensville Center Road
Cleveland, Ohio 44122

Please send Lecture Booklets checked above.

My check, payable to IARS in the amount of
$ ________ is enclosed.

________________________________
(Name)

________________________________
(Mail Address)

________________________________

________________________________
(City, State, Zip)

# IARS MEMBERSHIP

## FOR YOUR IN-TRAINING AND CONTINUING MEDICAL EDUCATION

The International Anesthesia Research Society is a non-profit, scientific and educational corporation of the State of Ohio, founded in 1922 "to foster progress and research in anesthesia." To this end the Society

Publishes the oldest journal in the specialty, *Anesthesia and Analgesia*

Sponsors an annual scientific meeting (Congress) which is held in March each year

Funds anesthesia-related research through the IARS B.B. Sankey Anesthesia Advancement Award

Membership in the IARS is voluntary; it is also separate and distinct from membership in any other local, state, regional or national anesthesia organization or association. Membership is open to individuals who qualify in the various categories shown below; who complete the appropriate application and submit it to the IARS Cleveland office with the applicable dues. All memberships include a subscription to *Anesthesia and Analgesia*. Members and Associate Members are entitled to a reduced registration fee at the IARS annual meeting; Educational Members pay no registration fee.

## . . . . MEMBERSHIP CATEGORIES . . . .

**MEMBERSHIP:** Open to individuals with doctorate degrees, who are licensed to practice in the medical, osteopathic, dental or veterinary medicine fields (i.e., MD, MB, DO, DDS, DMD, DVM); and to individuals with doctorate degrees in any scientific discipline (PhD), who are engaged in academic, private or commercial research.

**ASSOCIATE MEMBERSHIP:** Open to individuals in the allied health professions, duly certified by their professional accrediting organization as nurse anesthetists (CRNA); respiratory therapists or technicians (RRT or CRTT); physician/anesthesia assistants (PA/MMS); and other allied health professionals in anesthesia-related practice.

*Annual Dues for Members and Associate Members:* $45.00 U.S.; $55.00 foreign. These memberships are entered on a calendar year basis only.

**EDUCATIONAL MEMBERSHIP:** Open (with certification by program director) to doctors (interns/residents) enrolled in anesthesiology training programs; nurses enrolled in nurse anesthesia schools; students enrolled in programs leading to certification as physician assistants, respiratory therapists or technicians

*Annual Dues for Educational Members:* One-half of member rate. These memberships are entered in January or July for 2, 3, or 4 year periods. Applications, certified by program directors, must accompany check to cover full membership period.

- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -

International Anesthesia Research Society
3645 Warrensville Center Road, Cleveland, Ohio 44122, USA

Please send me ______ application(s) for: Membership (______)
Associate Membership (______)
Educational Membership (______)

Please print clearly: ________________________________________
Name and Degree (MD, DO, CRNA, RN, RRT, etc.)

________________________________________
Street Address City, State, Zip Code (country)

# Anesthesia and Analgesia

## Journal of the International Anesthesia Research Society

3645 Warrensville Center Road, Cleveland, Ohio 44122 Telephones: (216) 295-1124 or 295-1130

## Editorial Board

### Editor in Chief

Nicholas M. Greene, MD, New Haven, Connecticut

### Editors

David R. Bevan, MA, MB, BChir, Montreal, Quebec, Canada
D. Ryan Cook, MD, Pittsburgh, Pennsylvania
Michael J. Cousins, MD, FFARACS, FFARCS, Adelaide, South Australia
Benjamin G. Covino, PhD, MD, Boston, Massachusetts
Norig Ellison, MD, Philadelphia, Pennsylvania
Mieczyslaw Finster, MD, New York, New York
Alison B. Froese, MD, Kingston, Ontario, Canada
Edward D. Miller JR, MD, Charlottesville, Virginia
Daniel M. Philbin, MD, Boston, Massachusetts
Cedric Prys-Roberts, MA, DM, PhD, Bristol, United Kingdom
J. Gerald Reves, MD, Durham, North Carolina
John H. Tinker, MD, Iowa City, Iowa
K.C. Wong, MD, PhD, Salt Lake City, Utah

### Book Review Editor

Norig Ellison, MD, Philadelphia, Pennsylvania

Editorial correspondence and manuscripts should be addressed to: NICHOLAS M. GREENE, MD, Editor in Chief, *Anesthesia and Analgesia*, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510 (Telephone: 203-785-4703). For information concerning preparation of manuscripts see "A Guide for Authors" published quarterly in the Journal. All articles published in this Journal become the property of the International Anesthesia Research Society. Reproduction in whole or part is not permitted except by written consent of the publisher and the author.

Books for review should be sent directly to the Book Review Editor, NORIG ELLISON, MD, Department of Anesthesia, University of Pennsylvania, Philadelphia, Pennsylvania 19104.

Reprints: For single copies, write directly to the senior author at the address listed on the title page. Quantity orders (minimum 100) processed through ELSEVIER SCIENCE PUBLISHING CO, INC, 52 Vanderbilt Avenue, New York, NY 10017, prices on request.

The International Anesthesia Research Society is a nonprofit, scientific, and educational corporation in the state of Ohio. Members of the Board of Trustees of the Society are: Douglas B. Craig, MD, Bruce F. Cullen, MD, E. Paul Didier, MD, Judith H. Donegan, MD, PhD, Noel W. Lawson, MD, John T. Martin, MD, Emerson A. Moffitt, MD, Dean H. Morrow, MD, Robert K. Stoelting, MD, and John L. Waller, MD. Emeritus Trustees are: Paul R. Dumke, MD, Kenneth K. Keown, MD, Morris T. Nicholson, MD, B.B. Sankey, MD, and T. H. Seldon, MD.

*Anesthesia and Analgesia* (ISSN 0003-2999) is issued monthly for the IARS in one indexed volume per year by Elsevier Science Publishing Co, Inc, 52 Vanderbilt Avenue, New York, NY 10017. Printed in USA. © 1985 International Anesthesia Research Society. Second class postage paid at New York, NY and at additional offices.

Subscription information for 1985 applying to IARS members: USA and possessions, $45.00 per year, in all other countries $55.00. Membership is available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine, or other disciplines who are engaged in active clinical practice of or research in anesthesiology. ASSOCIATE MEMBERSHIP is available to individuals certified, licensed, or accredited in anesthesia-related professions (CRNA, CRTT, RRT, Physician Assistant). EDUCATIONAL MEMBERSHIP (half the full member price) is available to interns, residents, students in nurse anesthesia and related training programs, for a 2- or 3-year period only upon completion of application including certification by applicant's program director.

All membership payments and correspondence regarding IARS member subscriptions should be sent to: Emerson A. Moffitt, MD, Executive Secretary, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, Ohio 44122.

Subscription information for 1985 applying to non-IARS members: Institutions, $90.00. Outside of the USA and possessions, please add $10.00 for surface postage and handling. For airmail, add $38.00 in USA, Canada, and Mexico, $22.00 for surface airlift to Europe, $34.00 for surface airlift to Japan, and $88.00 for airmail to the rest of the world. Postmaster: Send address changes to: *Anesthesia and Analgesia*, Elsevier Science Publishing Co, Inc, 52 Vanderbilt Avenue, New York, NY 10017.

Orders and inquiries regarding institutional and nonmember individual subscriptions should be directed to: Journals Fulfillment, Elsevier Science Publishing Co, Inc, 52 Vanderbilt Avenue, New York NY 10017. Subscriptions are entered for the calendar year, January–December.

Correspondence inquiries regarding IARS member subscriptions should be sent to the IARS at the Cleveland, Ohio address above. Correspondence regarding all other subscriptions should be sent to Elsevier.

Advertising inquiries should be addressed to: Pharmaceutical Media, Inc, 130 Madison Avenue, New York, NY 10016. The appearance of advertising in publications of the International Anesthesia Research Society does not constitute a guarantee or endorsement of the quality or value of such product or of the claims made for it by its manufactuer. Discussions, views, and recommendations as to medical procedures, choice of drugs, and drug dosages are the responsibility of the authors. Every effort has been made to ensure the accuracy of the information. The editor, publisher, or the Society, however, must disclaim any responsibility or liability. Readers are advised to check package insert information for each drug before administration.

See classified ads section for submission of classified material.

Single issues: Single copy information available from Elsevier Science Publishing Co, Inc, upon request. Back volume (all issues prior to 1983) information available from IARS.

Anesthesia and Analgesia

# Contents

**Volume 64, Number 11, November 1985**

## SCIENTIFIC ARTICLES

High-Frequency Oscillatory Ventilation and Pulmonary Extravascular Water — *Masanori Tamura, Toshio Kawano, Ingrid Fitz-James, and A. Charles Bryan* — 1041

Inactivation of Atracurium in Human and Rat Plasma — *Vladimir Nigrovic, Jyoti B. Pandya, Melissa Auen, and Aron Wajskol* — 1047

Effects of Fentanyl and Diazepam in Dogs Deprived of Autonomic Tone — *Joan W. Flacke, L. Jane Davis, Werner E. Flacke, Byron C. Bloor, and Aaron P. Van Etten* — 1053

Electrophysiologic Effects of Enflurane and Halothane on Isolated Rabbit Hearts in the Presence and Absence of Metabolic Acidosis — *Suzuko Ozaki, Yasuyuki Gotoh, Haruaki Nakaya, Mitsue Azuma, and Morio Kanno* — 1060

Morphine Kinetics and Kidney Transplantation: Morphine Removal is Influenced by Renal Ischemia — *John Sear, Andrew Moore, Adrian Hunniset, Dene Baldwin, Michael Allen, Christopher Hand, Henry McQuay, and Peter Morris* — 1065

Effects of Glycine on Hemodynamic Responses and Visual Evoked Potentials in the Dog — *Janice Mei-li Wang, K. C. Wong, Donnell J. Creel, W. Matt Clark, and Shahram Shahangian* — 1071

Fentanyl Pharmacokinetics and Hemodynamic Effects in Preterm Infants during Ligation of Patent Ductus Arteriosus — *C. Collins, G. Koren, P. Crean, J. Klein, W. L. Roy, and S. M. MacLeod* — 1078

Heparin, Protamine, and Ionized Calcium In Vitro and In Vivo — *Hiroshi Goto, Tamio Kushihashi, Kirk T. Benson, Hitoshi Kato, Deanna K. Fox, and Kasumi Arakawa* — 1081

The Effect of Epidural Somatostatin on Postoperative Pain — *Joachim Chrubasik, Jacques Meynadier, Phillippe Scherpereel, and Erich Wünsch* — 1085

Bupivacaine-Induced Cardiotoxicity in Hypoxic and Acidotic Sheep — *Mark A. Rosen, Jarman W. Thigpen, Sol M. Shnider, Stanley E. Foutz, Gershon Levinson, and Minako Koike* — 1089

Age and the Solubility of Volatile Anesthetics in Ovine Tissues — *Jerrold Lerman, George A. Gregory, Mary M. Willis, Brigitte I. Schmitt, and Edmond I. Eger II* — 1097

## SCIENTIFIC ARTICLES—*continued*

A Double-Blind Comparison of Multiple Intramuscular Doses of Ciramadol, Morphine, and Placebo for the Treatment of Postoperative Pain — *W. Forrest Powell* — 1101

Continuous Monitoring of Arterial Oxygen Saturation with Pulse Oximetry during Transfer to the Recovery Room — *I. L. Tyler, Boonrak Tantisira, Peter M. Winter, and Etsuro K. Motoyama* — 1108

Intracranial Pressure after Atracurium in Neurosurgical Patients — *Michael D. Minton, Joseph A. Stirt, Robert F. Bedford, and Charles Haworth* — 1113

## REVIEW ARTICLE

Supplemental Medication for Ambulatory Procedures under Regional Anesthesia — *Beverly K. Philip* — 1117

## CLINICAL REPORTS

Development of Resistance to Pancuronium in Adult Respiratory Distress Syndrome — *Deborah L. Callanan* — 1126

Cardiac Arrest in a Child with an Anterior Mediastinal Mass — *H. Levin, S. Bursztein, and M. Heifetz* — 1129

Hepatic Necrosis Associated with Herpes Virus after Isoflurane Anesthesia — *Nancy A. Fisher, Robert T. Iwata, Edmond I. Eger II, and Edward A. Smuckler* — 1131

Loss of Radial Artery Pressure Trace During Internal Mammary Artery Dissection for Coronary Artery Bypass Graft Surgery — *John B. Kinzer, Peter R. Lichtenthal, and Leonard D. Wade* — 1134

# INTERNATIONAL ANESTHESIA RESEARCH SOCIETY
# 60th CONGRESS—March 15–19, 1986—
# Caesars Palace Hotel, Las Vegas, Nevada

## PRELIMINARY MEETING INFORMATION

**Program/Registration Mailing:** The preliminary program, with daily schedule of presentations, will be sent out in mid-December to all IARS members. This will include registration card, hotel card, social activities and spouse program. (IARS members outside of North America who plan to attend the meeting can receive this material by airmail upon request.) Non-IARS members who wish to receive meeting/membership information should contact the Cleveland office.

| | |
|---|---|
| Schedule: | Registration: Saturday, March 15—1–5 PM (continues daily)<br>Scientific Program: Sunday, March 16, through Wednesday, March 19<br>Exhibits: Sunday, March 16, through Tuesday, March 18 |
| Program: | • T.H. Seldon Distinguished Lecture—Dr. J. Alfred Lee, Essex, England<br>• 26 Review Course Lectures<br>• Panels: Outpatient Anesthesia, Cardiovascular Anesthesia<br>• Over 100 Scientific Papers<br>• Scientific Poster Presentations<br>• Theme Luncheon Sessions<br>• Scientific Exhibits |
| Technical (Commercial) Exhibits: | Including a number of company sponsored Product Seminars |
| Spouse Program: | "Effective Tax Strategies" Seminar; area tours and other activities and presentations of interest. |
| Reduced Air Fare: | A special discounted fare will be available through United Airlines for IARS registrants. |
| CME Credit: | AMA/ACCME Category 1 (31 hr, est.) AANA credit to be confirmed. |

---

SCIENTIFIC EXHIBITS: Applications for scientific exhibit space are available from the IARS office. There is no absolute deadline for submission of applications. However, availability of space in the exhibit area will be a factor in considering applications received after January 1, 1986.

ARTS AND CRAFTS EXHIBIT: Responding to interest expressed by a number of members, the IARS will for the first time include an arts and crafts exhibit at the 1986 meeting. If you or your spouse would like to enter your personally done art or craft work, the rules and entry blanks are available from the Cleveland office. **The deadline for entry is January 31, 1986.**

International Anesthesia Research Society
3645 Warrensville Center Road, Cleveland, OH 44122

Tel: (216) 295-1124

( ______ ) Please send rules and entry blank for Arts and Crafts Exhibit.
( ______ ) Please send application for Scientific Exhibit space.

(Name) ____________________
(Mail Address) ____________________
____________________

**Continuous $O_2$/$CO_2$ Monitoring Report #1**

**Subject:** Simple, low-cost pulse oximetry monitoring for timely hypoxemia detection.

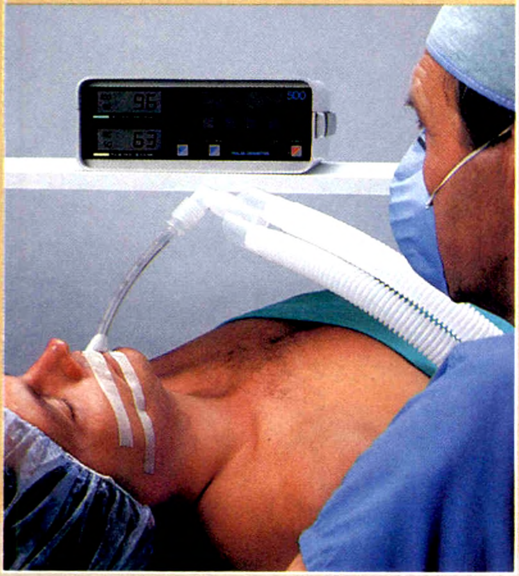
# 1

# Pulse Oximetry
# NOVAMETRIX 500

Pulse oximetry is a noninvasive technique for assessing patient oxygenation.

An oximeter determines percentage hemoglobin saturation by measuring the absorbency of two different wavelengths of light passed through a pulsating arterial vascular bed. By comparing the ratios of the pulse amplitudes from each light, $SaO_2$ may be calculated under a wide range of hemodynamic conditions.

The use of pulse oximetry during routine anesthesia allows early recognition of hypoxemia permitting quick response to improve oxygenation.



Accurate and reliable, pulse oximetry represents a significant advance in anesthesia monitoring. In designing the Model 500 Pulse Oximeter, Novametrix retained the accuracy and reliability of earlier units, but added two vital elements: ease of use and low cost.

The microprocessor-controlled Novametrix 500 Pulse Oximeter needs no calibration or warm-up. Its digital electronic circuitry is entirely maintenance-free.

Setup is fast. Just push the power switch and the unit performs a quick self-diagnostic check. Then the 500's programmed menu quickly helps you set the high and low $SaO_2$ and pulse rate limits. Once the limits are set they are constantly visible. And the Novametrix 500 keeps them in memory indefinitely—for weeks or even months—until you decide to change them.

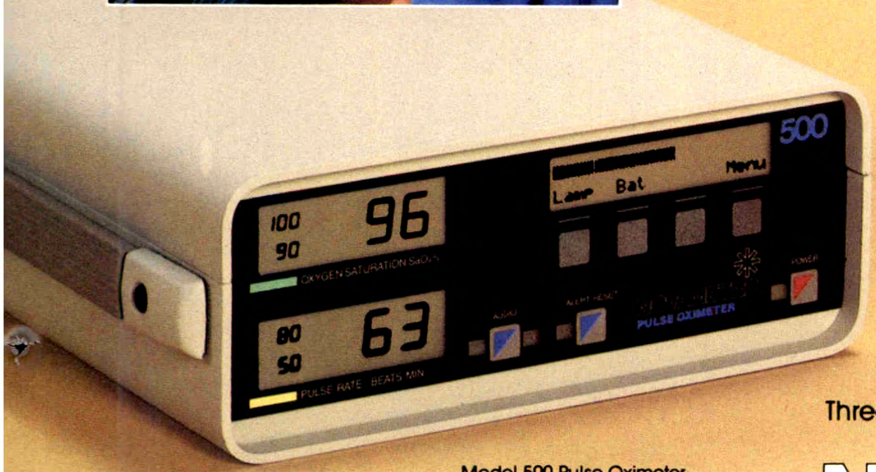
> ***"The Novametrix 500 is a simple, inexpensive means of monitoring oxygenation to reduce the incidence of anesthetic mishap during routine procedures."***

Operation is just as simple, with easy-to-read displays of $O_2$ saturation and pulse rate. A message center displays a bar graph of pulse amplitude as well as providing specific information regarding any alert condition. In addition, there's an audible pulse signal that changes in tone—up or down to reflect changes in $SaO_2$—so you can keep your eyes on the patient.

The Novametrix 500 Pulse Oximeter is small, lightweight (under 10 lbs.), and operates for a full 20 hours on a single battery recharge. (Not just an hour or two of battery backup power like most other oximeters.)

Novametrix finger, ear, and versatile flexible sensors are small, ruggedly built, and designed for easy application to patients of all ages. And Novametrix' unique selectable response time eliminates false alerts due to motion artifact.

For full technical details—and the surprisingly low price—write Novametrix Medical Systems Inc., 1 Barnes Industrial Park Road, P.O.Box 690, Wallingford, CT 06492. Or call us toll-free at 1-800-243-3444.



Model 500 Pulse Oximeter.

Pulse Oximetry.
End Tidal $CO_2$.
Transcutaneous $O_2$/$CO_2$.
Three technologies...one source.

**NOVAMETRIX**

# Introducing STRAPEZE™

## While others slip and slide all over the place, we've made a name for ourselves by staying put.

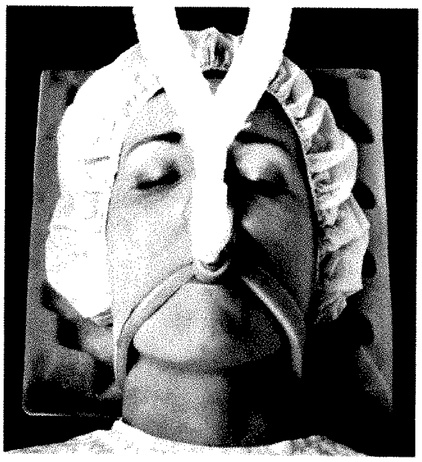
**No more fumbling for the tape. No more sticky adhesive devices. And no more concerns for the security and safety of your patient's airway. Now enjoy the speed, simplicity and protection of STRAPEZE.**

### Strap versus tape

Tape kinks, binds, and often loses its adhesive qualities under operating conditions. STRAPEZE, as its name implies, is a strap made of 100% non-allergenic Velfoam II®, a very durable and lightweight material with a foam core sandwiched between outer layers of soft, synthetic lambs-wool.

### So easy to apply

The STRAPEZE "one-step" fastening concept brings a new measure of assurance and security to endotracheal tube placement. And there's nothing else like it for ease of use. You simply attach one end of STRAPEZE to the tube, slip the strap behind the patient's neck, loop around tube and fasten with the Velcro tab back onto the strap's velvety surface. Job finished!



### Stays put—or it's not STRAPEZE!

Now you can forget about accidental extubations or bronchial intubations. STRAPEZE ensures precise and positive positioning of the tube. Where you put it, is where it stays. Which means the tube won't pull out, and it won't push down. Needless to say, such assurances can be a lifesaver.

### Another quality product from ProTechPacific

STRAPEZE was designed to answer the demanding needs of today's medical professional. Its innovative simplicity erases the tedium and uncertainty of performing an important task. And its specialized function is another example of ProTech Pacific's ongoing commitment to your profession. STRAPEZE. New convenience. New security. New comfort. And, for all these assurances, very inexpensive. For the comfort of the intubated patient, STRAPEZE is here to stay. Because it *stays put*.

*U.S. Patents pending*

**ProTechPacific**

*1221 Andersen Drive*
*San Rafael, California 94901*
*Call Toll Free: 800/227-0517*
*In Calif. 415/459-0745*

*Manufacturers of Protective Medical Products*

**Continuous $O_2/CO_2$ Monitoring Report #2**

**Subject:** Cost-effective capnography for the OR; calibration and condensation problems solved.

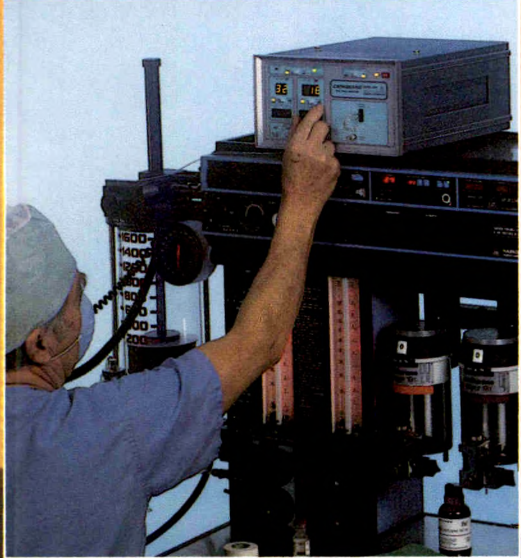
# 2

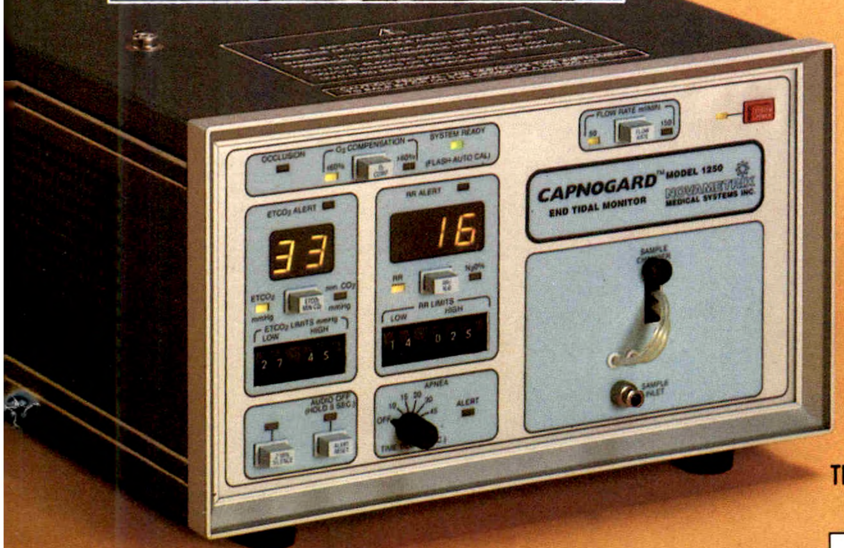
# End Tidal $CO_2$
# NOVAMETRIX 1250

---

The measurement of end tidal carbon dioxide by a modern on-line analyzer provides a close approximation of alveolar partial pressure of $CO_2$.

Continuous measurement of $ETCO_2$ in the OR allows up-to-the-minute assessment of the adequacy of ventilation, and assists in the timely diagnosis of intraoperative problems or metabolic trends allowing early intervention to prevent adverse outcome.





Capnogard 1250 End Tidal Monitor.

Capnography in the OR used to mean long warm-up periods, tedious calibration sessions, and a constant struggle to keep the sampling circuit clear of moisture.

Thanks to microelectronic technology, this is no longer the case. And none of the newer $ETCO_2$ monitors use this technology better than the Novametrix 1250.

But while the electronics of the Capnogard™ 1250 are complex, they actually make the monitor simpler to use. Push the system power switch and the unit is up and monitoring in less than two minutes. And its innovative microprocessor control system keeps it that way, ensuring continuous reliable operation.

> ***"An end tidal monitor you don't need to calibrate? Yes. The Capnogard 1250 from Novametrix."***

The designers of the Capnogard noted how moisture problems overwhelmed the water traps of even the best end tidal monitors. So they developed a dehumidification interface kit with a semipermeable tube drying system and a built-in disposable particulate filter. Then they incorporated a front panel accessible sample chamber that could be manually cleared in under a minute right in the OR. Moisture a problem with your end tidal monitoring? Not if you're using the Capnogard 1250.

And, thanks to the 1250's unique auto-zeroing system, you can forget about time-consuming daily calibration sessions. (Semi-annual reverification of calibration is recommended.)

Unlike many $CO_2$ analyzers, the 1250 was designed with the OR in mind. So you'll find features like direct measurement of $N_2O$; automatic and continuous $N_2O$ compensation; large LED readouts; apnea alert; two-minute silence, audio off, and alert reset buttons; sample exhaust for gas scavenging; and analog outputs for recorder and scope displays.

For details on the Capnogard 1250—and its surprisingly low price—write Novametrix Medical Systems Inc., 1 Barnes Industrial Park Road, P.O. Box 690, Wallingford, CT 06492. Or call us toll-free at 1-800-243-3444.

Pulse Oximetry.
End Tidal $CO_2$.
Transcutaneous $O_2/CO_2$.
Three technologies...one source.

**NOVAMETRIX**

## Now Published by Elsevier

# Journal of the American Geriatrics Society

GENE H. STOLLERMAN, MD, *Editor, Boston University Hospitals, Boston, MA*
JOHN P. BLASS, MD, PhD, *Associate Editor, White Plains, NY*

***Section Editors***

HARVEY J. COHEN, MD
*Geriatric Bioscience*
*Durham, NC*

DAVID C. THOMASMA, PhD
*Medical Ethics and Humanities*
*Maywood, IL*

JOHN R. BALL, MD, JD
*Law and Public Policy*
*Washington, DC*

URIEL S. BARZEL, MD
*Book Reviews*
*Bronx, NY*

PATRICK W. IRVINE, MD
*Abstracts*
*St. Paul, MN*

***Editorial Board***
***Through 1985***

ROBERT BERKOW, MD
*Lansdale, PA*
*Psychosomatic Medicine*

GEORGE E. BURCH, MD
*New Orleans, LA*
*Cardiology*

EWALD W. BUSSE, MD
*Durham, NC*
*Bio-behavioral Sciences*

LEO M. COONEY, Jr, MD
*New Haven, CT*
*Rheumatology and Rehabilitation*

WILLIAM R. HAZZARD, MD
*Baltimore, MD*
*Metabolism and Endocrinology*

PETER P. LAMY, PhD, FCP
*Baltimore, MD*
*Pharmacotherapy*

JAY P SANFORD, MD
*Bethesda, MD*
*Infectious Diseases*

IRVING S. WRIGHT, MD
*New York, NY*
*Cardiovascular Disease*

***Through 1986***

DARRELL R. ABERNETHY, MD
*Houston, TX*
*Clinical Pharmacology*

DANIEL BLAZER, MD
*Durham, NC*
*Psychiatry and Epidemiology*

CLAIR COX, MD
*Memphis, TN*
*Urology*

EDMUND PELLEGRINO, MD
*Washington, DC*
*Philosophy and Ethics of Medicine*

NICHOLAS J. PISACANO, MD
*Lexington, KY*
*Family Medicine*

JOHN ROWE, MD
*Boston, MA*
*Gerontologic Physiology*

DAVID SOLOMON, MD
*Los Angeles, CA*
*Endocrinology*

SHELDON TOBIN, PhD
*Albany, NY*
*Health Psychology*

***Through 1987***

EVAN CALKINS, MD
*Buffalo, NY*
*Geriatric Medicine*

EDWARD D. FROHLICH, MD
*New Orleans, LA*
*Hypertension and Clinical Pharmacology*

JOHN E. MORLEY, MD
*Sepulveda, CA*
*Neuroendocrinology*

ARTHUR J. MOSS, MD
*Rochester, NY*
*Cardiovascular Diseases*

LAURENCE Z. RUBENSTEIN, MD, MPH
*Sepulveda, CA*
*Geriatric Health Services*

ROBERT D. TERRY, MD
*La Jolla, CA*
*Neuropathology*

STANLEY F. WAINAPEL, MD
*Boston, MA*
*Rehabilitation Medicine*

CHARLES E. WELLS, MD
*Nashville, TN*
*Psychiatry*

**Journal of the American Geriatrics Society** has been providing the medical community with outstanding original coverage of all aspects of geriatrics for over 30 years. Emphasizing original research, **Journal of the American Geriatrics Society** publishes both clinical and basic science studies on a broad range of topics. A distinguished editorial board, drawn from many medical specialties, ensures that the journal includes contributions from all areas of this interdisciplinary field.

Regular features of **Journal of the American Geriatrics Society** include:

- **Medical Ethics and Humanities**
  thought-provoking viewpoints on the difficult ethical questions facing all physicians who treat the elderly
- **Law and Public Policy**
  clear, concise reports on the latest legislative and judicial developments that affect patient management
- **Clinical Experience**
  practical solutions to common problems in geriatric health care delivery

Geriatricians, internists, cardiologists, rheumatologists, psychiatrists, endocrinologists, family practitioners, and others who treat older patients rely on **Journal of the American Geriatrics Society** for up-to-date information on all aspects of geriatric health care.

**Journal of the American Geriatrics Society** is abstracted/indexed in *Index Medicus, Current Contents, Science Citation Index, Automatic Subject Citation Alert, Social Sciences Citation Index*, and *ISI/Biomed.*

**1985 Subscription Information:**
**Journal of the American Geriatrics Society**
Volume 33, 12 issues, 1985
Personal Rate: $50.00
Institutional Rate: $55.00
Subscribers outside the U.S. and U.S. possessions should add $15.00 for surface delivery or $30.00 for air mail delivery. **Sample copies are available.**

**Elsevier**

## ORDER FORM

**Journal of the American Geriatrics Society**
Volume 33, 12 issues, ISSN 0002-8614, 1985

________ Please enter my subscription at the Institutional Rate of $55.00
________ Please enter my subscription at the Personal Rate of $50.00
________ Please send me a free sample copy.

Subscribers outside the U.S. and U.S. possessions should add $15.00 for surface delivery or $30.00 for air mail delivery.

**Payment**
**Enclosed please find my:** ☐ personal check ☐ bank draft
☐ UNESCO coupons in the amount of ________
**Please charge to:** ☐ American Express ☐ VISA
☐ MasterCard/Access/Eurocard (issuing bank # ________)

Account # ________ Expires ________

Signature ________

☐ **Please bill me.** (Orders from non-U.S. customers must be prepaid.)

Name ________
Institution ________
Address ________
City ________
State ________ Zip/Postal Code ________

For sample copies, send to
**in North and South America:**
Elsevier Science Publishing Co., Inc.
P.O. Box 1663, Grand Central Station, New York, NY 10163
**in the rest of the world:**
Elsevier Science Publishers, Direct Mail Department
P.O. Box 211, 1000 AE Amsterdam, The Netherlands

**Note: Send subscription orders to either your usual supplier or the New York address.** All subscriptions begin with the first issue of the calendar year. Subscription rates valid through Dec. 31, 1985. 7/85 EB329

**Continuous $O_2$/$CO_2$ Monitoring Report #3**

**Subject:** Compact, easy-to-use $P_{tc}O_2$ monitoring for OR patients.

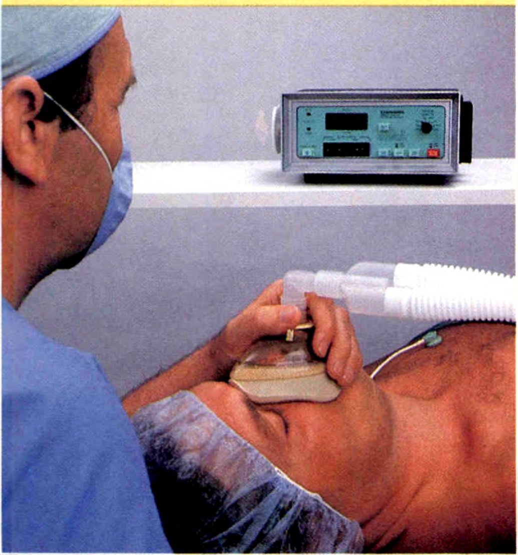
## 3

## Transcutaneous $O_2$
# NOVAMETRIX 811

"$P_{tc}O_2$ is a useful variable because it is a noninvasive 'global' monitor of patient oxygenation. It can give an early warning of decreasing oxygen delivery, thus allowing the treatment of impending hypoxia before it occurs." [1]

"$P_{tc}O_2$ monitoring proved also to act as an early warning device for impending hypoxemia and hemodynamic compromise, thereby facilitating very early therapeutic intervention." [2]

1 Barker, S. M.D., Ph.D. and Tremper, K. M.D., Ph.D. *Journal of Clinical Monitoring, 1:* 130-134 (1985).
2 Chubra-Smith, N.M. M.D., et. al. *Anesthesia/Analgesia 64:* 185-304 (1985).



Along with a growing recognition of the usefulness of continuous gas monitoring during surgery came the need for a cost-effective $P_{tc}O_2$ monitor suitable for routine use on patients in the OR. The Novametrix 811 monitor meets that need.

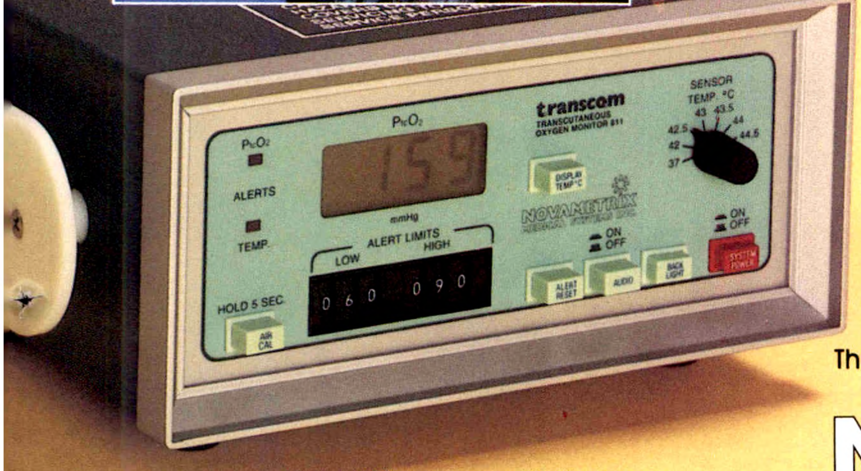
Simplicity is a key feature of the Novametrix 811. Activate the system power switch, push the automatic air calibration button, and you're ready to monitor.

And Novametrix knows that space is scarce in a crowded OR, so the 811 is compact and can be equipped for pole mounting. The 811 is also a true portable transcutaneous monitor, and may be operated on AC power or on its rechargeable gel cell for up to eight hours between recharges.

***"The Novametrix 811 is the first transcutaneous monitor to deal with the special requirements of all OR patients."***

An eight-position temperature selection switch offers a choice of sensor temperatures for operation. Visual display of both actual and selected temperature provides reassurance of proper sensor operation. And while we're talking about sensors, remember that Novametrix sensors are recognized for their rugged construction and durability, so you can count on their withstanding the occasional rough handling they'll receive in the OR.

For complete information on the Novametrix Model 811 Transcutaneous $O_2$ monitor, along with details on its surprisingly low price, call us toll-free at 1-800-243-3444. Or write Novametrix Medical Systems Inc., 1 Barnes Industrial Park Road, P.O. Box 690, Wallingford, CT 06492.



Model 811 Transcutaneous $O_2$ Monitor.

Pulse Oximetry.
End Tidal $CO_2$.
Transcutaneous $O_2$/$CO_2$.
Three technologies...one source.

NOVAMETRIX

# Albumin & PPF are no safer or more effective than Hespan®

(hetastarch)

*...they're simply*

A 12 ©1985 American Critical Care

## As safe as albumin or PPF

In comparative clinical studies, platelet counts, hematocrits, serum fibrinogen levels, prothrombin times (PT), and partial thromboplastin times (PTT) seen with Hespan were comparable to those seen with albumin or plasma protein fraction (PPF).[1,2]

Other studies demonstrate that when any reduction in platelet count or prolongation of PT or PTT does occur with Hespan, no increased bleeding results, even in patients with multiple trauma.[3-5] As with any volume expander, patients should be monitored for excessive hemodilution of coagulant factors or circulatory overload when large volumes are administered.

When Hespan-treated patients were monitored to detect localized or systemic sepsis, there was no evidence of a decrease in their ability to ward off infection or combat an established infection.[5]

Hespan is nonantigenic and, as with blood-derived colloids, any risk of allergic reaction is minimal. Hespan also has a negligible effect on subsequent blood typing or crossmatching.[6]

## As effective as albumin or PPF

Comparative clinical studies have repeatedly demonstrated that Hespan is as effective as albumin or PPF in postoperative myocardial revascularization,[1-3] and hemorrhagic, traumatic, or septic shock.[4,5,7]

No significant differences between Hespan and albumin or PPF were noted in any efficacy parameter.[1-5,7] Hespan effectively maintained colloid osmotic pressure, restored plasma volume, and improved cardiac output and renal function in hypovolemic patients.[1-5,7] And, the volume-expanding effect of a single infusion of Hespan can persist for 24 hours or longer.

## Half the price of albumin or PPF

Hespan offers a potential savings to your hospital of tens of thousands of dollars a year.

double the price.

Hespan®
(6% hetastarch in 0.9% sodium chloride injection)
Hespan
6% hetastarch in 0.9% sodium chloride injection
Hespan (Hetastarch)

For additional information, contact the Medical Services Department, American Critical Care, 1600 Waukegan Road, McGaw Park, IL 60085. Phone 1-800-323-4980.

**Lifesaving, moneysaving**

**HESPAN®**
(hetastarch)

**American Critical Care**

American Hospital Supply Corporation

*Please see references and brief summary of prescribing information on following page.*

**References: 1.** Diehl JT, Lester JL, Cosgrove DM: Clinical comparison of hetastarch and albumin in postoperative cardiac patients. *Ann Thorac Surg 34* (6):674-679, 1982. **2.** Moggio RA, Rha CC, Somberg ED, et al: Hemodynamic comparison of albumin and hydroxyethyl starch in postoperative cardiac surgery patients. *Crit Care Med 11* (12):943-945, 1983. **3.** Kirklin JK, Lell WA, Kouchoukos NT: Hydroxyethyl starch versus albumin for colloid infusion following cardiopulmonary bypass in patients undergoing myocardial revascularization. *Ann Thorac Surg 37* (1):40-46, 1984. **4.** Puri VK, Paidipaty B, White L: Hydroxyethyl starch for resuscitation of patients with hypovolemia and shock. *Crit Care Med 9* (12):833-837, 1981. **5.** Shatney CH, Deepika K, Militello PR, et al: Efficacy of hetastarch in the resuscitation of patients with multisystem trauma and shock. *Arch Surg 118*:804-809, 1983. **6.** Daniels MJ, Strauss RG, Smith-Floss AM: Effects of hydroxyethyl starch on erythrocyte typing and blood crossmatching. *Transfusion 22* (3):226-228, 1982. **7.** Rackow EC, Falk JL, Fein IA, et al: Fluid resuscitation in circulatory shock: A comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. *Crit Care Med 11*(11):839-850, 1983.

**HESPAN®** (hetastarch)

**6% Hetastarch in 0.9% Sodium Chloride Injection**

***CONTRAINDICATIONS***

Hetastarch is contraindicated in patients with severe bleeding disorders or with severe congestive cardiac and renal failure with oliguria or anuria.

***WARNINGS***

Large volumes may alter the coagulation mechanism. Thus, administration of hetastarch may result in transient prolongation of prothrombin, partial thromboplastin and clotting times. With administration of large doses, the physician should also be alert to the possibility of transient prolongation of bleeding time.

Hematocrit may be decreased and plasma proteins diluted excessively by administration of large volumes of hetastarch.

***Usage in Leukapheresis:*** Significant declines in platelet counts and hemoglobin levels have been observed in donors undergoing repeated leukapheresis procedures due to the volume expanding effects of hetastarch. Hemoglobin levels usually return to normal within 24 hours. Hemodilution by hetastarch and saline may also result in 24 hour declines of total protein, albumin, calcium and fibrinogen values.

***Usage in Pregnancy:*** Reproduction studies have been done in mice with no evidence of fetal damage. Relevance to humans is not known since hetastarch has not been given to pregnant women. Therefore, it should not be used in pregnant women, particularly during early pregnancy, unless in the judgment of the physician the potential benefits outweigh the potential hazards.

***Usage in Children:*** No data available pertaining to use in children.

The safety and compatibility of additives have not been established.

***PRECAUTIONS***

The possibility of circulatory overload should be kept in mind. Special care should be exercised in patients who have impaired renal clearance since this is the principal way in which hetastarch is eliminated. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Indirect bilirubin levels of 0.83 mg% (normal 0.0-0.7 mg%) have been reported in 2 out of 20 normal subjects who received multiple hetastarch infusions. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering hetastarch to patients with a history of liver disease.

Regular and frequent clinical evaluation and laboratory determinations are necessary for proper monitoring of hetastarch use during leukapheresis. Studies should include CBC, total leukocyte and platelet counts, leukocyte differential count, hemoglobin, hematocrit, prothrombin time (PT), and partial thromboplastin time (PTT).

Hetastarch is nonantigenic. However, allergic or sensitivity reactions have been reported (see ADVERSE REACTIONS). If such reactions occur, they are readily controlled by discontinuation of the drug and, if necessary, administration of an antihistaminic agent.

***ADVERSE REACTIONS***

The following have been reported: vomiting, mild temperature elevation, chills, itching, submaxillary and parotid glandular enlargement, mild influenza-like symptoms, headaches, muscle pains, peripheral edema of the lower extremities, and anaphylactoid reactions consisting of periorbital edema, urticaria, and wheezing.

***HOW SUPPLIED***

NDC **0094-0037-05-Hespan*** (6% Hetastarch in 0.9% Sodium Chloride Injection) is supplied sterile and nonpyrogenic in 500 ml intravenous infusion bottles.

***CAUTION***

Federal (U.S.A.) law prohibits dispensing without prescription. Rev: Feb., 1982

Distributed by

**American Critical Care**

American Hospital Supply Corporation
McGaw Park, IL USA 60085

**This Publication is available in Microform.**

**University Microfilms International**

Please send additional information

for ______________________
(name of publication)

Name______________________

Institution______________________

Street______________________

City______________________

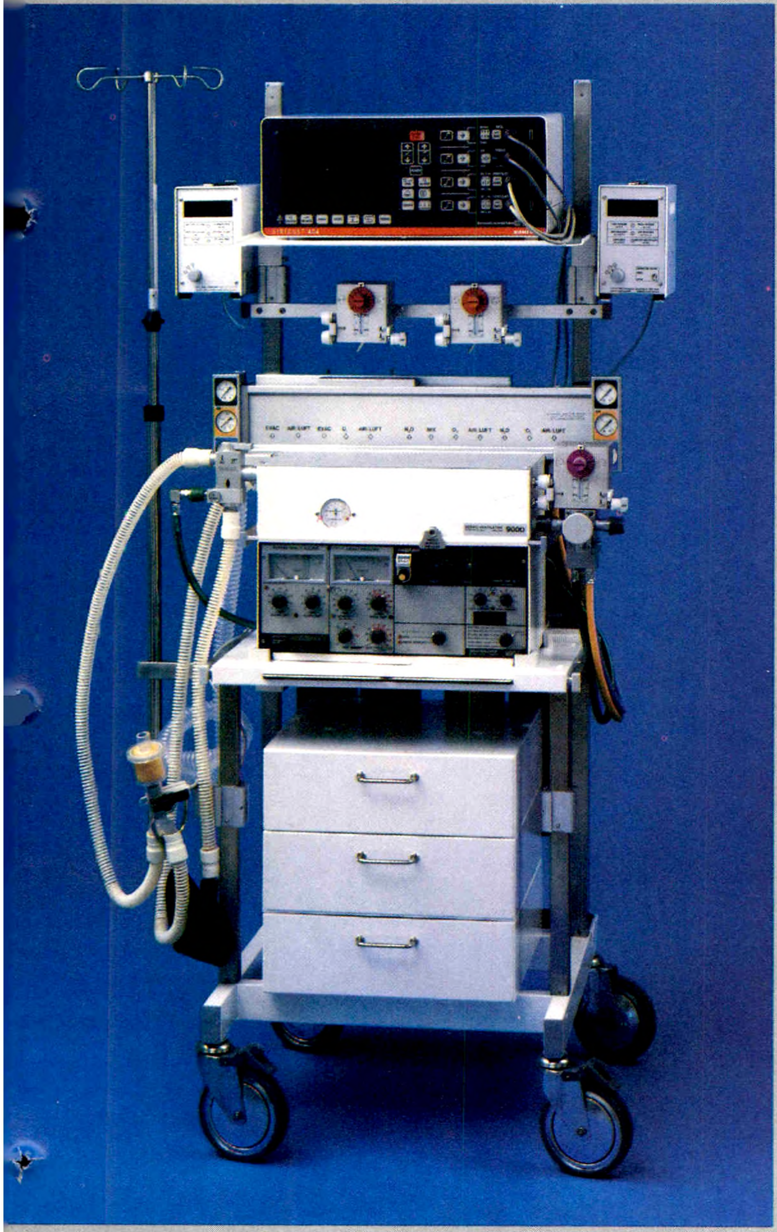
State____________ Zip____________

300 North Zeeb Road
Dept. P.R.
Ann Arbor, Mi. 48106

**SIEMENS**

Introducing the Servo Anesthesia System

**The advanced anesthesia system for pediatric and adult patients.**



Now there's one highly versatile anesthesia system designed for routine and critical care cases involving pediatric as well as adult patients. It's the new Servo Anesthesia System from Siemens. Compact and modular in design, the system is human-engineered for ease of operation and highly accurate control...plus maximum safety.

**New versatility and efficiency in the OR**
The system utilizes our Servo Ventilator, offering the most advanced technology available for both volume-controlled and pressure-supported anesthesia applications. A new ventilation mode, pressure support, enables patients to breathe spontaneously with the assistance of a predetermined pressure. The system continuously monitors all important functions and provides instantaneous readings and audible/visual alarms.

**Advanced monitoring interface**
The Servo Anesthesia System interfaces with a broad range of exclusive, innovative monitoring systems, including the $CO_2$ Analyzer 930, the Lung Mechanics Calculator 940 and the Sirecust 404.

**New ease of maintenance**
You're assured of quality performance with a minimum of maintenance. The system requires only minimal servicing; the costs are extraordinarily low. And best of all, most maintenance is easily performed right on site by members of your own staff. No costly off-site service!

And you're further assured of immediate professional assistance, if necessary, from your Siemens sales and service representatives. It's all part of the Siemens commitment to superior products and systems for healthcare professionals and their patients.

For further information, contact Siemens-Elema Ventilator Systems, 2360 No. Palmer Dr., Schaumburg, Illinois 60195—(312) 397-5975, or call toll-free 1-800-323-1281.

**Siemens...a pioneer in innovative healthcare systems.**

Siemens-Elema Ventilator Systems,
2360 No. Palmer Dr., Schaumburg, IL 60195
☐ Please send me information on Servo Anesthesia System.
Name
Institution
Address
City
State
Zip

MG/5820-009 WLM 174

# INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

## THE B.B. SANKEY IARS ANESTHESIA ADVANCEMENT AWARD

The B.B. Sankey Anesthesia Advancement Award has been established to expand upon and replace the IARS Research Award. This new award is intended to foster investigative efforts in the fields of anesthesia research, clinical care, education and administration.

The recipients of the 1985 Sankey Anesthesia Advancement Awards are:

Roger S. Brett, MD, PhD, State University of New York, Stony Brook, New York
Patrick Curling, MD, Emory University School of Medicine, Atlanta, Georgia
Richard F. Davis, MD, University of Florida College of Medicine, Gainesville, Florida

## 1986 B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

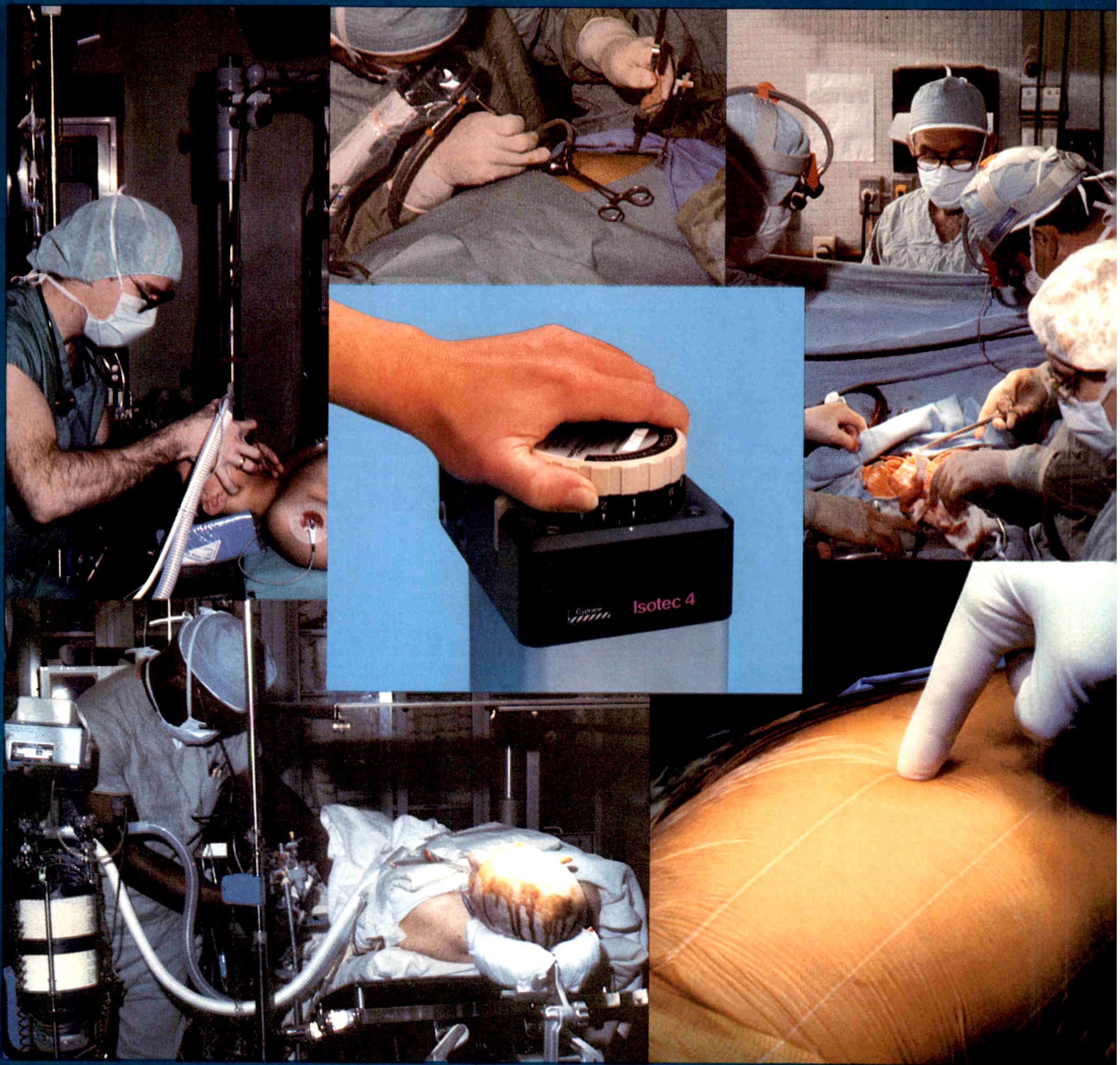
Applications for up to $25,000 are invited for the 1986 Award, subject to the following basic conditions:

- The proposal must be within the general field of anesthesiology and may be for research, clinical care, education or administration.
- The applicant must be a member of the International Anesthesia Research Society.
- Applications must be received in the IARS Cleveland office not later than December 16, 1985.
- The official application form for the award must be used. This form, as well as the guidelines for applicants, is available on request to:

Emerson A. Moffitt, MD
Executive Secretary
International Anesthesia Research Society
3645 Warrensville Center Road
Cleveland, Ohio 44122, USA
Telephone: (216) 295-1124

The 1986 Award(s) will be announced at the Annual Meeting (60th Congress) of the International Anesthesia Research Society to be held at Caesars Palace, Las Vegas, Nevada, March 15–19, 1986.

# Forane® (isoflurane)
# The Versatile Anesthetic



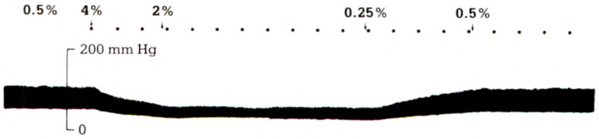
**Anaquest**

Forane® (isoflurane)

# **Forane**® (isoflurane) The Versatile Anesthetic

## A hypotensive agent for craniotomy and clipping of aneurysms

Isoflurane may be used as both anesthetic and hypotensive agent, providing for precise control of blood pressure throughout procedures such as clipping of cerebral aneurysms.[1]



Blood pressure tracing demonstrating the rapid response of systemic blood pressure to changes in inspired isoflurane concentration. The arrows indicate the changes in isoflurane concentration and the dots mark 1-min intervals. Mean blood pressure during the normotensive period was 70 mm Hg and 40 mm Hg during the hypotensive phase.[1]

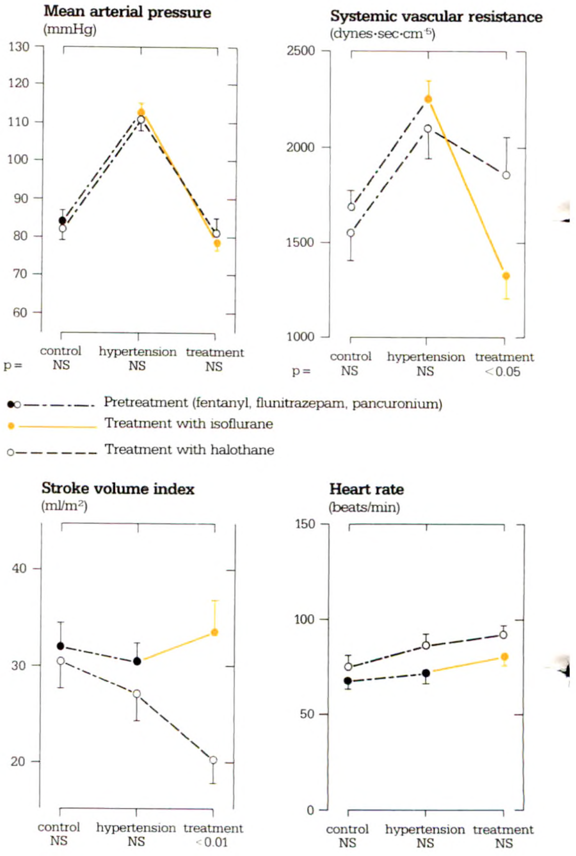
## Control of intracranial pressure for craniotomy and excision of space-occupying lesion

Isoflurane causes no increase in intracranial pressure (ICP) when $PaCO_2$ is controlled at 25-30 torr, and ICP may be readily lowered *during surgery* by decreasing $PaCO_2$.[2]

## Control of hypertension during coronary artery bypass surgery

Control of intraoperative hypertension may be achieved with isoflurane by lowering peripheral vascular resistance (left ventricular afterload) generally without depressing stroke volume or increasing heart rate. These effects can be of particular benefit in patients with compromised left ventricular function. Halothane is equally effective in lowering blood pressure without increasing heart rate, but it decreases stroke volume.

Treatment of hypertension with either isoflurane or halothane anesthesia in patients undergoing coronary artery bypass surgery (Adapted from Hess et al[3]).



## Potentiation of relaxants for orthopedic surgery

With isoflurane anesthesia, profound surgical muscle relaxation can be provided with one-third to two-thirds the usual relaxant dose (pancuronium, d-tubocurarine or atracurium).[4,5] Thus the recovery period may be shortened and the need for reversal agents reduced by the rapid elimination of isoflurane.

## Stability of heart rhythm when full hemostatic doses of epinephrine are needed

"Isoflurane, like enflurane, produces stable cardiac rhythm and, unlike halothane, does not sensitize the myocardium to the effects of catecholamines."[6]

## A rapid recovery with few post-anesthetic symptoms for outpatient surgery

"Isoflurane is eliminated more rapidly than any other potent modern inhaled anesthetic."[7] (Blood-gas partition coefficient, only 1.4)

Anesthesia using isoflurane in a mixture of oxygen and air produced a significantly lower incidence of nausea and vomiting following outpatient laparoscopy than anesthesia that included nitrous oxide.[8]

**Post-laparoscopy Nausea (N) and Vomiting (V)**

| Group | No. of Patients | No. of Patients with N or N&V |
|---|---|---|
| fentanyl, $N_2O$, $O_2$ | 37 | 23 (62%)* |
| isoflurane, fentanyl, $O_2$ | 20 | 6 (30%) |
| isoflurane, $O_2$ | 20 | 5 (25%) |

Adapted from Alexander et al[8]  *$p<0.05$

**References:**

1. Lam AM, Gelb AW: Cardiovascular effects of isoflurane-induced hypotension for cerebral aneurysm surgery. Anesth Analg 62:742-748, 1983.
2. Adams RW et al: Isoflurane and cerebrospinal fluid pressure in neurosurgical patients. Anesthesiology 54:97-99, 1981. 3. Hess W et al: Comparison of isoflurane and halothane when used to control intraoperative hypertension in patients undergoing coronary artery bypass surgery. Anesth Analg 62:15-20, 1983. 4. Miller RD et al: Comparative neuromuscular effects of pancuronium, gallamine, and succinylcholine during Forane and halothane anesthesia in man. Anesthesiology 35:509-514, 1971. 5. Tracrium® (atracurium besylate) prescribing information, Burroughs Wellcome Co., Research Triangle Park, NC 27709. 6. Wade JG, Stevens WC: Isoflurane: an anesthetic for the eighties? Anesth Analg 60(9):666-682, 1981.
7. Eger EI II: Isoflurane, a compendium and reference, Ohio Medical Anesthetics, Madison, WI, 1981. 8. Alexander GD et al: The role of nitrous oxide in postoperative nausea and vomiting. Anesth Analg 63:175, 1984.

For complete use information, please see following page.

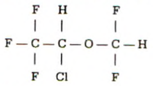
**Forane® . . . a product of original Anaquest research**
(isoflurane)

# Forane®...The Versatile Anesthetic
## (isoflurane)

CAUTION: Federal Law Prohibits Dispensing without Prescription

**DESCRIPTION**

FORANE (isoflurane) is a nonflammable general inhalation anesthetic agent. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:



$$F-\overset{F}{\underset{F}{C}}-\overset{H}{\underset{Cl}{C}}-O-\overset{F}{\underset{F}{C}}-H$$

Some physical constants are:

| | | |
|---|---|---|
| Molecular weight | | 184.5 |
| Boiling point at 760 mm Hg | | 48.5 °C (uncorr.) |
| Refractive index $n_D^{20}$ | | 1.2990-1.3005 |
| Specific gravity 25 °/25 °C | | 1.496 |
| Vapor pressure in mm Hg** | 20 °C | 238 |
| | 25 °C | 295 |
| | 30 °C | 367 |
| | 35 °C | 450 |

**Equation for vapor pressure calculation:

$$\log_{10}P_{vap} = A + \frac{B}{T} \quad \text{where:} \quad A = 8.056,\ B = -1664.58,\ T = °C + 273.16\ (\text{Kelvin})$$

| | |
|---|---|
| Partition coefficients at 37 °C | |
| Water/gas | 0.61 |
| Blood/gas | 1.43 |
| Oil/gas | 90.8 |
| Partition coefficients at 25 °C - rubber and plastic | |
| Conductive rubber/gas | 62.0 |
| Butyl rubber/gas | 75.0 |
| Polyvinyl chloride/gas | 110.0 |
| Polyethylene/gas | ~2.0 |
| Polyurethane/gas | ~1.4 |
| Polyolefin/gas | ~1.1 |
| Butyl acetate/gas | ~2.5 |
| Purity by gas chromatography | >99.9% |
| Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec. and 23 °C | None |
| Lower limit of flammability in oxygen or nitrous oxide at 900 joules/sec. and 23 °C | Greater than useful concentration in anesthesia. |

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave U.V. light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

**CLINICAL PHARMACOLOGY**

FORANE (isoflurane) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is as follows:

| Age | 100% Oxygen | 70% $N_2O$ |
|---|---|---|
| 26 ± 4 | 1.28 | 0.56 |
| 44 ± 7 | 1.15 | 0.50 |
| 64 ± 5 | 1.05 | 0.37 |

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal $PaCO_2$, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administered epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 mL of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE, THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

**Pharmacokinetics:** Isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

**INDICATIONS AND USAGE**

FORANE (isoflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

**CONTRAINDICATIONS**

Known sensitivity to FORANE (isoflurane) or to other halogenated agents.

Known or suspected genetic susceptibility to malignant hyperthermia.

**WARNINGS**

Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions.

FORANE (isoflurane) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

**PRECAUTIONS**

**General:** As with any potent general anesthetic, FORANE (isoflurane) should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

**Information to Patients:** Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

**Laboratory Tests:** Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

**Drug Interactions:** Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of $N_2O$.

See CLINICAL PHARMACOLOGY.

**Carcinogenesis:** Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at 1/2, 1/8 and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice which were given the same background gases, but not the anesthetic.

**Pregnancy Category C:** Isoflurane has been shown to have a possible anesthetic-related fetotoxic effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

**Malignant Hyperthermia:** In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the $CO_2$ absorption system (hot canister). $PaO_2$ and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

**ADVERSE REACTIONS**

Adverse reactions encountered in the administration of FORANE (isoflurane) are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting and ileus have been observed in the postoperative period. As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia.

**OVERDOSAGE**

In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

**DOSAGE AND ADMINISTRATION**

**Premedication:** Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

**Inspired Concentration:** The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for isoflurane;
b) vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula:

$$\%\ \text{isoflurane} = \frac{100\ P_V\ F_V}{F_T\ (P_A - P_V)}$$

where:
$P_A$ = Pressure of atmosphere
$P_V$ = Vapor pressure of isoflurane
$F_V$ = Flow of gas through vaporizer (mL/min)
$F_T$ = Total gas flow (mL/min)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

**Induction:** Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbiturate. Inspired concentrations of 1.5 to 3.0% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

**Maintenance:** Surgical levels of anesthesia may be sustained with a 1.0 to 2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5 to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

**HOW SUPPLIED**

FORANE (isoflurane), NDC 10019-360-40, is packaged in 100 mL amber-colored bottles.

**Storage:** Store at room temperature. Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

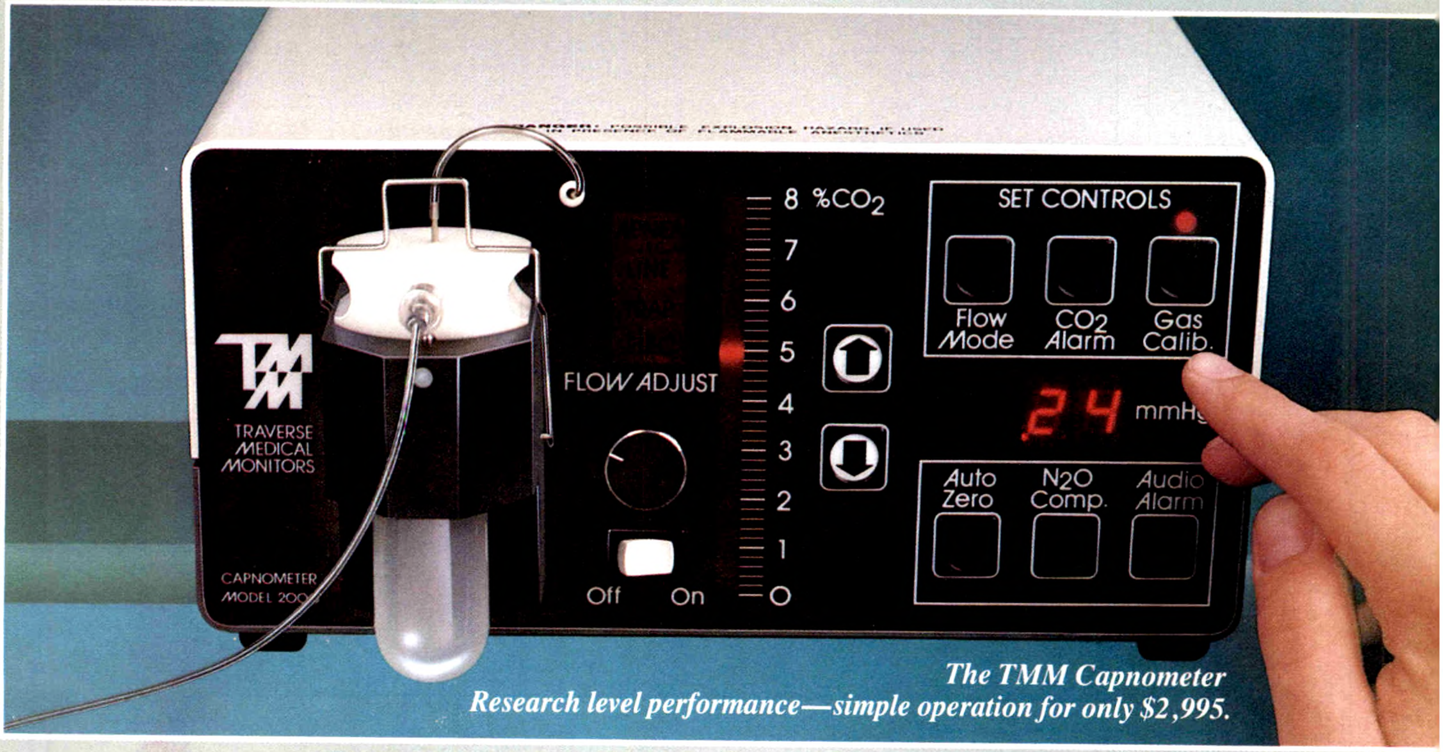
A-0117 Revised 5-84

**Anaquest** Forane® (isoflurane)

Anaquest
2005 West Beltline Highway
Madison WI 53713 2318
608 273 0019
Telex 910 286 2792
A Division of BOC Inc

BOC Health Care

# Forget your old ideas about capnometers.



*The TMM Capnometer*
*Research level performance—simple operation for only $2,995.*

# Ours is easy to use.

The TMM Capnometer is simple to operate. Just connect the Capnometer to the patient or the ventilator circuit, and turn it on. To set parameters, as illustrated by the gas calibration procedure above, you simply press tactile response buttons.

Thanks to a powerful microprocessor, the TMM Capnometer monitors itself so you can give more attention to your patient. The Capnometer alerts you when a trend has been determined that deviates from parameters you have established.

All user selected operating parameters are retained in memory. Automatic baseline updates provide long term unattended operation.

Data display is clear, bright, and continuous. A linearized signal output enables you to observe end-tidal waveforms.

An advanced Fluids Separator* on the TMM Capnometer continuously clears the gas stream of fluids.

A reliable infrared analyzer counts $CO_2$ molecules in under 100 msec at a flow rate of 260 ml/minute—a rate comparable to dedicated mass spectrometers and faster than multiplexed units.

The TMM Capnometer is backed by a comprehensive user support and service program. And it costs only $2,995.

Traverse
Medical
Monitors
TMM™
A
SUBSIDIARY OF
DYNATECH CORPORATION

*For more information, please contact:*
*Traverse Medical Monitors, 6812 South State Road, Saline, Michigan 48176*
*or call toll-free: (800) 247-7038 (800) 722-4153 in Michigan*

*patent pending

# NITROUS OXIDE/$N_2O$

Editor: **Edmond I. Eger II, M.D.,** Professor and Vice Chairman for Research, Department of Anesthesia, University of California, San Francisco

After 140 years of use, nitrous oxide is now known to be more than an inert vehicle for other, more potent anesthetics. Nitrous oxide affects the function of every body tissue significantly. Optimum application requires a full appreciation of both the benefits and potential hazards of this anesthetic substance.

***Nitrous Oxide/$N_2O$*** is a complete resource on the subject. It describes what is known about nitrous oxide – applications and contraindications – and debates its continued clinical use. The current clinical applications of $N_2O$ are reviewed by means of:

- thorough discussion of $N_2O$ pharmacology and distribution
- detailed summary of known side effects and toxicity
- practical guidelines for avoiding and managing these effects

Finally, the case for administering this anesthetic is carefully and candidly assessed in chapters by proponents of both views. ***Nitrous Oxide/$N_2O$*** is a controversial work that everyone using the drug will want to read.

Order from your usual supplier or
Elsevier Science Publishing Co., Inc.
P.O. Box 1663, Grand Central Station, New York, NY 10163

**Contents.** Preface. Contributors. A History of Nitrous Oxide. Physics, Chemistry, and Manufacture of Nitrous Oxide. Nitrous Oxide Analgesia. MAC. Nitrous Oxide Delivery Systems. Pharmacokinetics. Respiratory Effects of Nitrous Oxide. Cardiovascular Effects of Nitrous Oxide. Central Nervous System Effects of Nitrous Oxide. Neuromuscular Effects of Nitrous Oxide. Nitrous Oxide in Obstetrics. Metabolism of Nitrous Oxide. Nitrous Oxide Inactivates Methionine Synthetase. Mutagenicity, Carcinogenicity, and Teratogenicity of Nitrous Oxide. Nitrous Oxide Abuse. Toxicity of Nitrous Oxide. The Use of Nitrous Oxide by Dentists. Nitrous Oxide in Veterinary Practice and Animal Research. Controlling Occupational Exposure to Nitrous Oxide. Should We Not Use Nitrous Oxide. We Should Continue to Use Nitrous Oxide. Epilogue. Index.

1984 416 pages 0-444-00860-8 cloth $37.50
(Distributed outside the U S A and Canada by Edward Arnold Ltd., London.)

**ELSEVIER**

**Note:** Price subject to change without notice.
In NY State please add applicable sales tax.

EB 248

---

# Canadian Anaesthetists' Society Journal

An International Anaesthesia Journal publishing reports of investigation, clinical reports, review articles and other features. Published bi-monthly.

Now With a Continuing Medical Education Section in each Journal issue!

**CME topics scheduled for 1985**

- Anaesthetic Considerations in the Burn Patient
- Anaesthesia and the Aged
- Calcium Channel Blockers
- Haemodynamic Monitoring
- Anaesthetic Circuits
- Malignant Hyperthermia

Plus An Annual Meeting Supplement is published as Part II of each May issue. The Supplement contains refresher course outlines and abstracts of papers presented in the scientific programme of the Annual Meeting of the Canadian Anaesthetists' Society.

**1985 Subscription Rates** (Canadian Dollars)

☐ Individual $55.00 ☐ Institutional $75.00 ☐ Air Mail (optional) $30.00

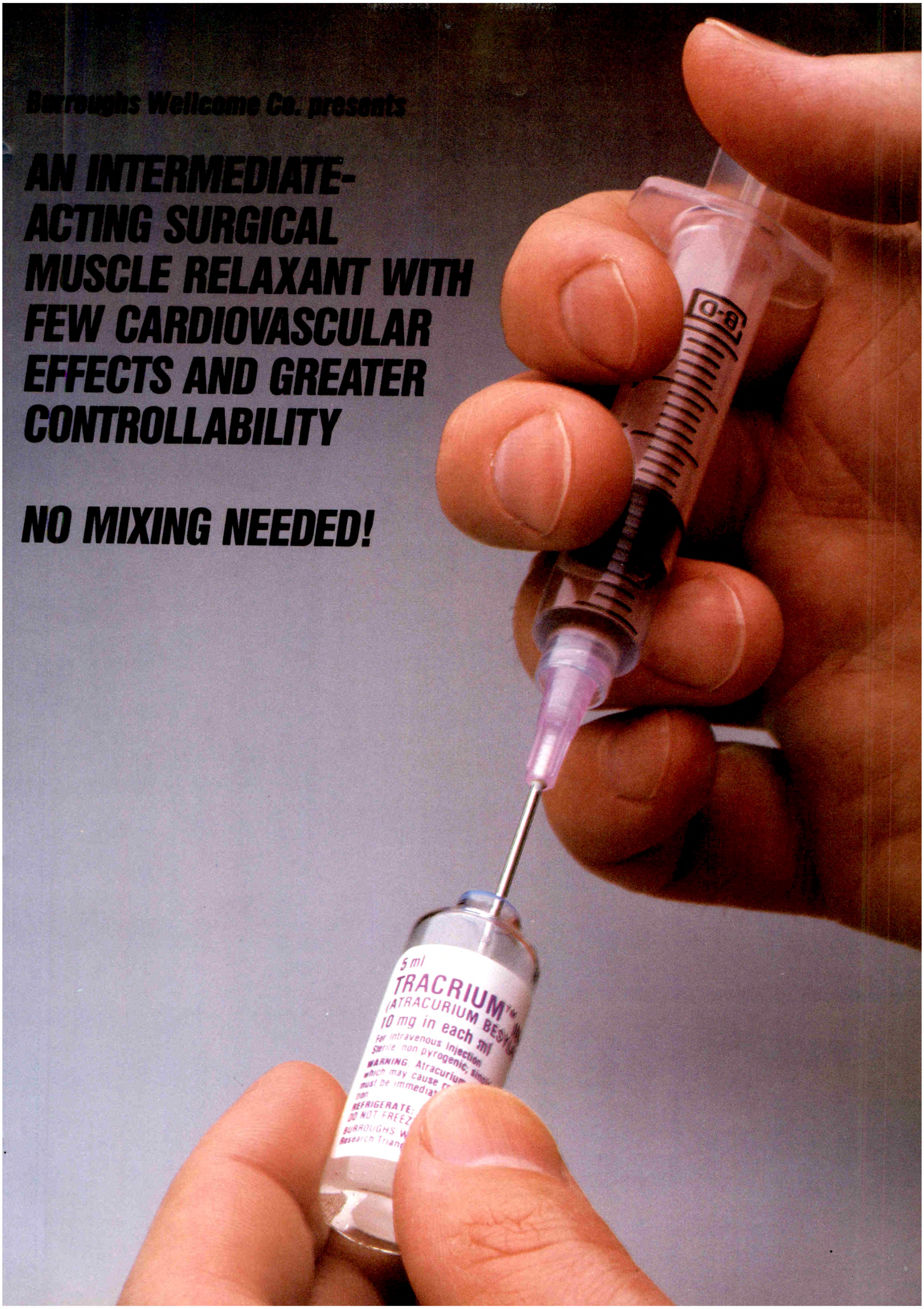
☐ Payment Enclosed ☐ Bill to Credit Card Account ☐ VISA ☐ MasterCard

Account ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ Exp. Date Signature Date

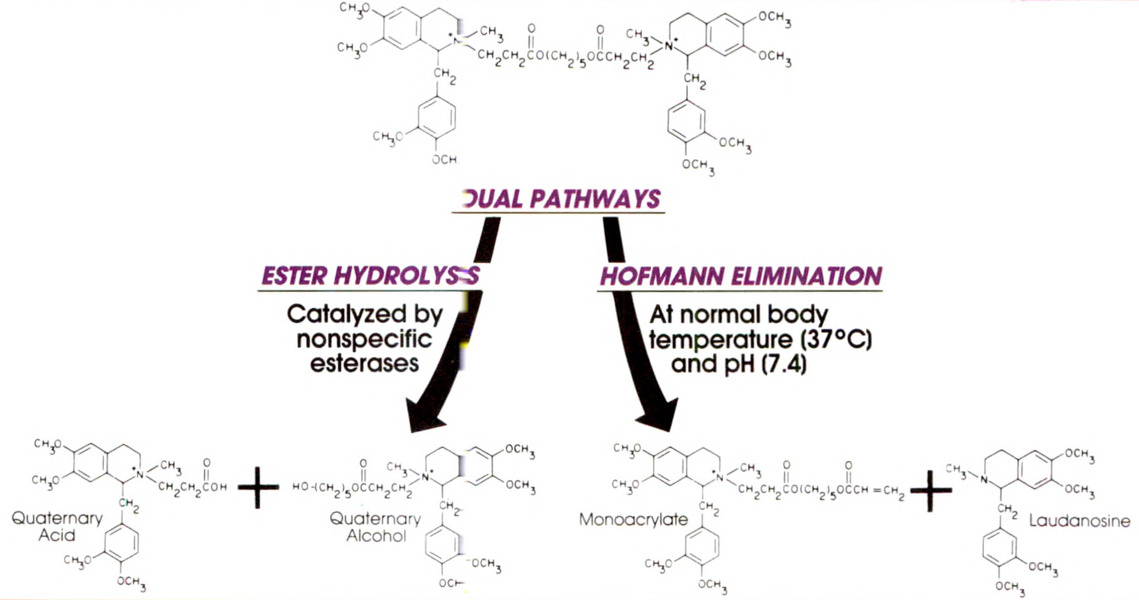
Name

Address

**Mail to:** Canadian Anaesthetists' Society Journal, 94 Cumberland Street, Suite 901, Toronto, Ontario, Canada M5R 1A3


Burroughs Wellcome Co. presents
AN INTERMEDIATE-ACTING SURGICAL MUSCLE RELAXANT WITH FEW CARDIOVASCULAR EFFECTS AND GREATER CONTROLLABILITY
NO MIXING NEEDED!
0·8
5 ml
TRACRIUM™
(ATRACURIUM BESYL
10 mg in each ml
For intravenous injection
Sterile, non pyrogenic,
WARNING Atracurium
which may cause
must be immedia
REFRIGERATE:
DO NOT FREEZ
BURROUGHS W
Research Trian

# UNIQUE METABOLISM PROVIDES BETTER PREDICTABILITY, ALLOWING BETTER CONTROL



☐ *Tracrium® Injection (atracurium besylate) is inactivated by two nonoxidative pathways that are not dependent on kidney or liver function:*

1 *Hofmann elimination—a nonenzymatic process that occurs at physiologic temperature and pH*

2 *Ester hydrolysis—catalyzed by nonspecific esterases; normal levels of plasma cholinesterase are not required*

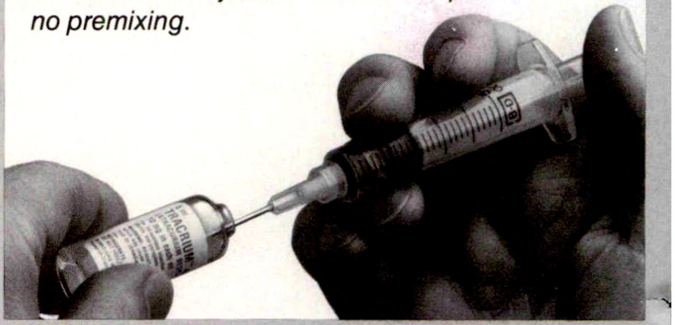
*These attributes make Tracrium a more flexible surgical muscle relaxant—it may be tailored to a wide variety of surgical cases.*

*"Atracurium has the special feature of being broken down to inactive products by the Hofmann elimination reaction. This means that the active drug can be removed from the biophase by other means not totally dependent on enzyme action, redistribution or excretion."*[1]

*"At present, no other available muscle relaxant undergoes this kind of degradation at physiologic pH."*[2]

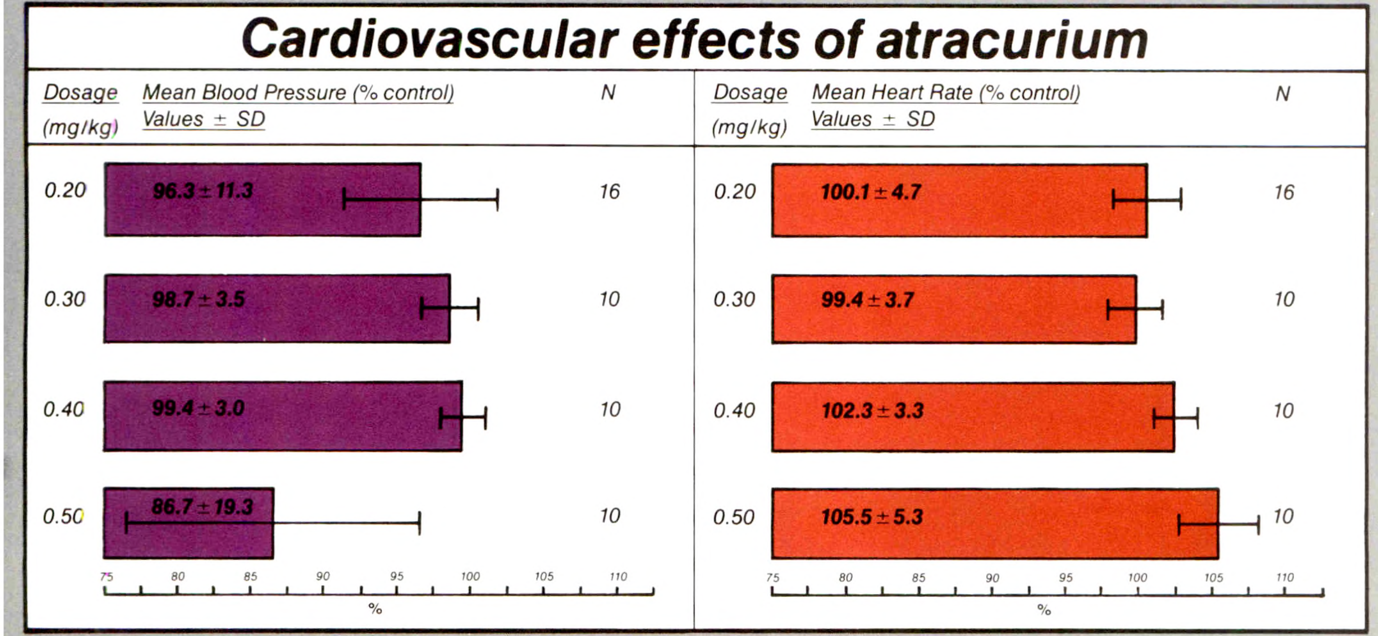
## Convenient and Ready to Use

*Tracrium is easily administered—requires no premixing.*



## Few Cardiovascular Effects at Recommended Dosages

☐ *Tracrium® (atracurium besylate) produces virtually no clinically significant cardiovascular hemodynamic changes when administered at recommended dosage levels—a significant benefit in patients with compromised cardiac ability or cardiac risk.*


Cardiovascular effects of atracurium

Adapted from Basta et al.[3]

## No Cumulative Effects Upon Recovery, After Multiple Doses

☐ *Repeated equipotent doses of Tracrium, administered at equal points of recovery, have no cumulative effect on recovery time*

☐ *Once recovery begins, it is relatively rapid and independent of dose*

☐ *This means that you do not have to calculate progressively smaller doses for repeat administration, and that recovery is more consistent and predictable*

*"One patient received 12 successive doses of atracurium after recovering completely from the initial dose, yet the 25%-75% recovery times were 10.0 and 12.2 min, respectively. This may indicate that atracurium is not cumulative...."[1]*

## Minimal Histamine Release

☐ *Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine*

☐ *Clinically significant histamine release occurs well within the clinical dosage range (at $ED_{95}$) for curare, at the upper limits of the clinical dosage range (at 2 × $ED_{95}$) for metocurine and outside the clinical dosage range (at 3 × $ED_{95}$) for atracurium[4]*

☐ *The lack of hemodynamic changes due to Tracrium suggests minimal histamine release*

*Please see brief summary of prescribing information on the following page.*

*REFERENCES:*

*1. Ali HH, Savarese JJ, Basta SJ, et al: Clinical pharmacology of atracurium: A new intermediate acting nondepolarizing relaxant. Seminars in Anesthesia 1982; 1:57-62.*

*2. Katz RL, Stirt J, Murray AL, et al: Neuromuscular effects of atracurium in man. Anesth Analg 1982; 61:730-734.*

*3. Basta SJ, Ali HH, Savarese JJ, et al: Clinical pharmacology of atracurium besylate (BW 33A): A new non-depolarizing muscle relaxant. Anesth Analg 1982; 61:723-729.*

*4. Basta SJ, Savarese JJ, Ali HH, et al: Histamine-releasing potencies of atracurium besylate (BW 33A), metocurine, and d-tubocurarine. Anesthesiology 1982;57:A261.*

**TRACRIUM® INJECTION**
(atracurium besylate)

*Copr. © 1984 Burroughs Wellcome Co. All rights reserved.*

# TRACRIUM® INJECTION
## (atracurium besylate)

This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

**DESCRIPTION:** Tracrium (atracurium besylate) is an intermediate-duration, nondepolarizing, skeletal muscle relaxant for intravenous administration.

**INDICATIONS AND USAGE:** Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

**CONTRAINDICATIONS:** Tracrium is contraindicated in patients known to have a hypersensitivity to it.

**WARNINGS:** TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

**PRECAUTIONS:**

**General:** Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine. The possibility of substantial histamine release in sensitive individuals must be considered however. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

**You'll get the latest facts on**
**TRACRIUM® INJECTION**
**(atracurium besylate)**
**at**
**The New York State**
**Society of Anesthesiologists**
**PGA in Anesthesiology**

**New York, NY**
**December 14-17, 1985**

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome or other neuromuscular diseases or in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

**Drug Interactions:** The neuromuscular blocking action of Tracrium may be enhanced by enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; or quinidine.

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenesis and fertility studies have not been performed. Atracurium was evaluated in a battery of three short term mutagenicity tests. It was non-mutagenic in both the Ames Salmonella assay at concentrations up to 1000 μg/plate, and in a rat bone marrow cytogenicity assay at up to paralyzing doses. A positive response was observed in the mouse lymphoma assay under conditions (80 and 100 μg/ml, in the absence of metabolic activation) which killed over 80% of the treated cells; there was no mutagenicity at 60 μg/ml and lower, concentrations which killed up to half of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations (1200 μg/ml and higher) which also killed over 80% of the treated cells. Mutagenicity testing is intended to simulate chronic (years to lifetime) exposure in an effort to determine potential carcinogenicity. Thus, a single positive mutagenicity response for a drug used infrequently and/or briefly is of questionable clinical relevance.

**Pregnancy: *Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in children below the age of 2 years have not been established.

**ADVERSE REACTIONS:** Tracrium produced few adverse reactions during extensive clinical trials, most of which were suggestive of histamine release (see PRECAUTIONS section). The overall incidence of clinically important adverse reactions was 7/875 or 0.8%.

Approximately one million patients received Tracrium during the first year following introduction to the U.S. market in December, 1983. Spontaneously reported adverse reactions were uncommon (approximately 0.02%). The following adverse reactions are among those most frequently reported, but there are insufficient data to support an estimate of their incidence:

**Musculoskeletal:** Inadequate block, prolonged block
**Cardiovascular:** Hypotension, vasodilatation (flushing), tachycardia, bradycardia
**Respiratory:** Dyspnea, bronchospasm, laryngospasm
**Integumentary:** Rash, urticaria, reaction at injection site

**DOSAGE AND ADMINISTRATION:** Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

A Tracrium dose of 0.4 to 0.5 mg/kg, given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically acceptable neuromuscular blockade under balanced anesthesia generally lasts 20 to 35 minutes; recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

An initial Tracrium dose of 0.3 to 0.4 mg/kg is recommended following the use of succinylcholine for intubation under balanced anesthesia.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg; with halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria. Maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anesthesia, slightly longer under isoflurane or enflurane.

An initial Tracrium dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for patients with significant cardiovascular disease and for patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated.

No Tracrium dosage adjustments are required for patients with renal disease or for pediatric patients two years of age or older. In pediatric patients, maintenance doses may be required with slightly greater frequency than in adults.

**HOW SUPPLIED:** Tracrium Injection, 10 mg atracurium besylate in each ml. Ampuls of 5 ml (50 mg atracurium besylate per ampul). Box of 10 ampuls (NDC-0081-0940-10).

10 ml Multiple Dose Vial (100 mg atracurium besylate per vial). The multiple dose vial contains 0.9% benzyl alcohol added as a preservative. Box of 10 (NDC-0081-0940-95).

Store under refrigeration at 2° to 8°C (36° to 46°F); DO NOT FREEZE.

U.S. Patent No. 4179507

Printed in U.S.A.

**TRACRIUM® INJECTION**
*(atracurium besylate)*

Wellcome
**Burroughs Wellcome Co.**
Research Triangle Park
North Carolina 27709

84TRA8E

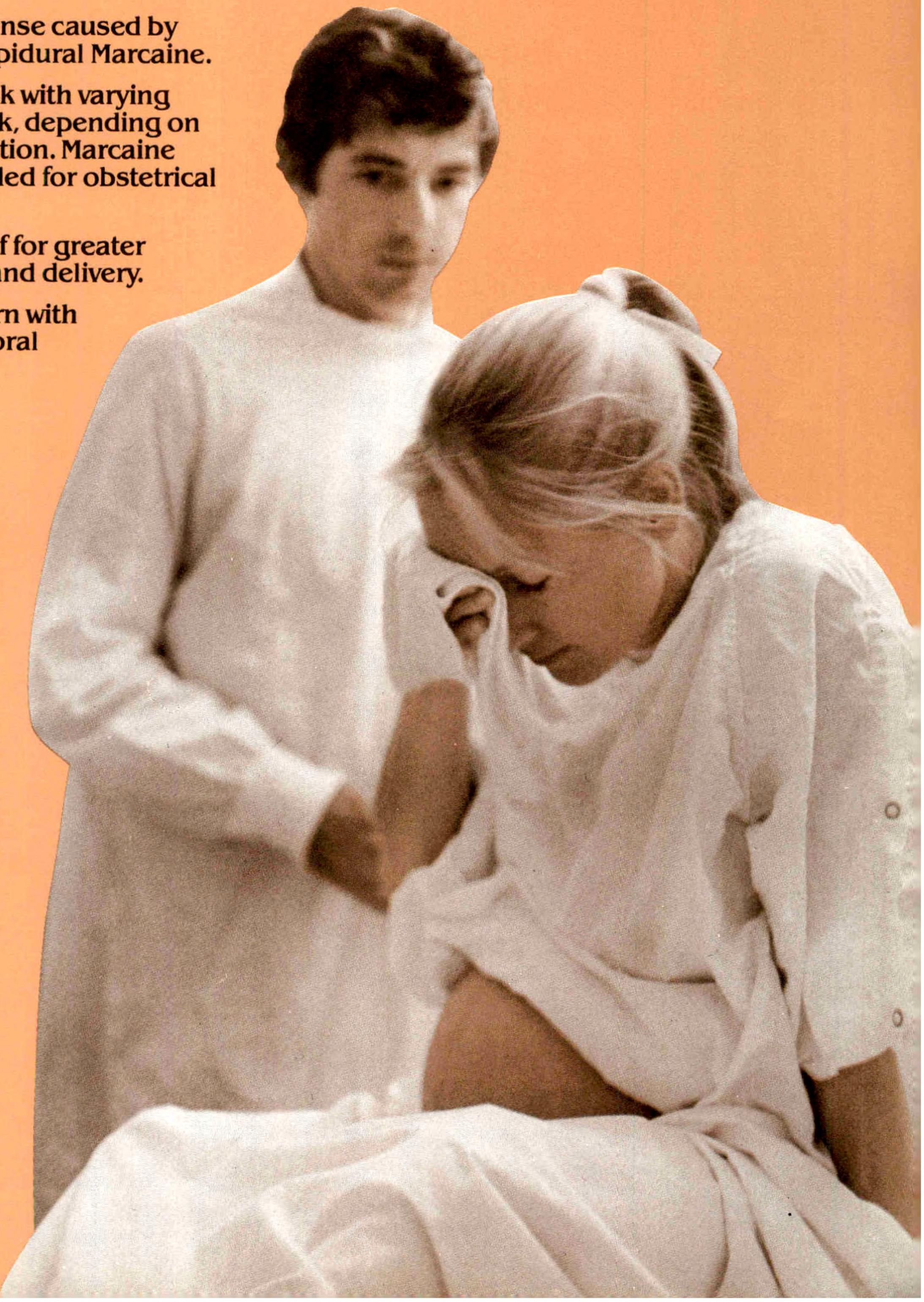
# Reduce Maternal and Fetal Stress.

## Marcaine® HCl 0.25% or 0.5%

(bupivacaine HCl injection, USP)

with or without epinephrine 1:200,000

- Break the stress response caused by unblocked pain with epidural Marcaine.
- Excellent sensory block with varying degrees of motor block, depending on dosage and concentration. Marcaine 0.75% not recommended for obstetrical anesthesia.
- Long lasting pain relief for greater comfort during labor and delivery.
- Proven safe for newborn with minimal neurobehavioral effects and minimal drug exposure.[1,2]



**Winthrop-Breon**

**WINTHROP-BREON LABORATORIES**
90 Park Avenue, New York, NY 10016

See adjacent page for important product information concerning contraindications, warnings, adverse reactions, patient selection, and prescribing and precautionary recommendations.

Resuscitative equipment and drugs should be readily available when any local anesthetic is used.

Contraindicated for obstetric paracervical block.

©1984 Winthrop-Breon Laboratories

# Marcaine® HCl
## (bupivacaine HCl injection, USP) with or without epinephrine 1:200,000

**PLEASE CONSULT FULL PRESCRIBING INFORMATION. A SUMMARY FOLLOWS:**

**CONTRAINDICATIONS:** Obstetric paracervical block anesthesia; use in this technique has resulted in fetal bradycardia and death. Known hypersensitivity to the drug or to any amide-type local anesthetic, or to other components of MARCAINE solutions.

**WARNINGS**

> **THE 0.75% CONCENTRATION OF MARCAINE IS NOT RECOMMENDED FOR OBSTETRICAL ANESTHESIA. THERE HAVE BEEN REPORTS OF CARDIAC ARREST WITH DIFFICULT RESUSCITATION OR DEATH DURING USE OF MARCAINE FOR EPIDURAL ANESTHESIA IN OBSTETRICAL PATIENTS. IN MOST CASES, THIS HAS FOLLOWED USE OF THE 0.75% CONCENTRATION. RESUSCITATION HAS BEEN DIFFICULT OR IMPOSSIBLE DESPITE APPARENTLY ADEQUATE PREPARATION AND APPROPRIATE MANAGEMENT. CARDIAC ARREST HAS OCCURRED AFTER CONVULSIONS RESULTING FROM SYSTEMIC TOXICITY, PRESUMABLY FOLLOWING UNINTENTIONAL INTRAVASCULAR INJECTION. THE 0.75% CONCENTRATION SHOULD BE RESERVED FOR SURGICAL PROCEDURES WHERE A HIGH DEGREE OF MUSCLE RELAXATION AND PROLONGED EFFECT ARE NECESSARY.**

**LOCAL ANESTHETICS SHOULD ONLY BE EMPLOYED BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES WHICH MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED, AND THEN ONLY AFTER INSURING THE *IMMEDIATE* AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY RESUSCITATIVE EQUIPMENT, AND THE PERSONNEL RESOURCES NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES. (See also ADVERSE REACTIONS, PRECAUTIONS and OVERDOSAGE.) DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST AND, POSSIBLY, DEATH.**

Local-anesthetic solutions containing antimicrobial preservatives, ie, those supplied in multiple-dose vials, should not be used for epidural or caudal anesthesia because their safety has not been established with regard to intrathecal injection—intentionally or not.

It is essential that aspiration for blood or cerebrospinal fluid, where applicable, be done prior to injecting any local anesthetic (the original and all subsequent doses) to avoid intravascular or subarachnoid injection, which can occur even with a negative aspiration.

MARCAINE with epinephrine 1:200,000 or other vasopressors should not be used concomitantly with ergot-type oxytocic drugs, and used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types; severe prolonged hypertension may result.

Pending further experience, MARCAINE administration in children younger than 12 years is not recommended.

Mixing, or a prior or intercurrent use, of any other local anesthetic with MARCAINE cannot be recommended because such use lacks sufficient clinical data.

There have been reports of cardiac arrest and death with MARCAINE for intravenous regional anesthesia (Bier block). Since information on safe dosages and procedural techniques is lacking, MARCAINE is not recommended.

**PRECAUTIONS: General:** Safety and effectiveness of local anesthetics depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Resuscitative equipment, drugs, and oxygen should be available for immediate use. (See WARNINGS, ADVERSE REACTIONS, OVERDOSAGE.) During major regional nerve blocks, the patient should have I.V. fluids via an indwelling catheter to assure a functioning intravenous pathway. The lowest effective anesthetic dosage should be used to avoid high plasma levels and serious adverse effects.

**Epidural Anesthesia:** The 0.5% and 0.75% solutions should be administered in increments of 3-5 mL with sufficient time between doses to detect toxic manifestations of unintentional intravascular or intrathecal injection. Administration should be slow, with frequent aspirations before and during the procedure to avoid intravascular injection which is still possible even if aspirations for blood are negative. Syringe aspirations should also be performed before and during each supplemental injection by "continuous" (intermittent) catheter technique. During an epidural procedure, it is recommended that a test dose be administered initially and the effects monitored before giving the full dose. When using continuous catheter technique, test doses should be given prior to both the original and all reinforcing doses because plastic tubing in the epidural space can migrate (etc., as in package insert). Clinical conditions permitting, the test dose should contain epinephrine (10-15 μg has been suggested) to provide warning of unintended intravascular injection. If injected into a blood vessel, this amount is likely to produce a transient "epinephrine response" within 45 seconds, consisting of an increase in heart rate and/or systolic blood pressure, circumoral pallor, palpitations, and nervousness in the unsedated patient who may exhibit only a pulse-rate increase of 20 or more beats per minute for 15 or more seconds. Therefore, following the test dose, heart rate should be monitored for any increase. Patients on beta blockers may not manifest such changes, but blood-pressure monitoring can detect a transient systolic rise. The test dose should also contain 10-15 mg of MARCAINE or an equivalent amount of another local anesthetic to detect unintended intrathecal injection. This will be evidenced within a few minutes by signs of spinal block (eg, decreased gluteal sensation, paresis of the legs or, in the sedated patient, absent knee jerk). Two or 3 mL of MARCAINE 0.5% with epinephrine 1:200,000 contain, respectively, 10 and 15 mg of bupivacaine HCl and 10 and 15 μg of epinephrine. An intravascular or subarachnoid injection is still possible even with negative results of the test dose, which itself may produce an epinephrine-induced cardiovascular or systemic toxic reaction or high spinal effect.

Repeated doses may cause significant increases in plasma levels with each such injection due to slow accumulation of the drug or its metabolites, or to slow metabolic degradation. Tolerance to elevated blood levels varies with the patient's status. Debilitated, elderly, and acutely ill patients should be given reduced doses commensurate with age and physical status. Also use local anesthetics with caution in patients with hypotension or heart block.

There should be careful and constant monitoring of the patient's cardiovascular and respiratory (adequacy of ventilation) vital signs and state of consciousness after each injection, and kept in mind at such times that restlessness, anxiety, incoherent speech, lightheadedness, numbness and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, twitching, depression, or drowsiness may be warnings of CNS toxicity.

Local anesthetic solutions with a vasoconstrictor should be used cautiously and carefully in body areas supplied by end arteries or with otherwise restricted blood supply (digits, nose, external ear, penis, etc.). Patients with hypertensive vascular disease may exhibit exaggerated vasoconstrictor response; ischemic injury or necrosis may result.

Amide-type anesthetics such as MARCAINE are metabolized by the liver; these drugs (especially repeat doses) should be used cautiously in patients with hepatic disease. Because of an inability to metabolize local anesthetics normally, patients with severe hepatic disease are at greater risk of developing toxic plasma concentrations. Also use with caution in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the drug's prolongation of A-V conduction.

Serious dose-related cardiac arrhythmias may occur if preparations containing epinephrine are employed in patients during or following administration of potent inhalation anesthetics. In deciding whether to use these agents concurrently, their combined action on the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection should be taken into account (when applicable).

Many drugs used in anesthesia conduction are potentially triggering agents for familial malignant hyperthermia. Because it is unknown whether amide-type anesthetics may trigger this reaction and because the need for supplemental general anesthesia cannot be predicted in advance, it is suggested that a standard management protocol be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure, and metabolic acidosis may precede temperature elevation. Successful outcome is dependent on early diagnosis, prompt discontinuance of the suspect triggering agent(s), and prompt treatment including oxygen, dantrolene I.V. (see prescribing information before use), and other supportive measures.

**Use in Head and Neck Area:** Small doses of local anesthetics injected into the area, including retrobulbar, dental, and stellate ganglion blocks, may produce adverse reactions similar to systemic toxicity seen with unintentional intravascular injections of larger doses. Confusion, convulsions, respiratory depression and/or respiratory arrest, and cardiovascular stimulation or depression have been reported and may be due to intraarterial injection of the local anesthetic with retrograde flow to the cerebral circulation. Patients receiving these blocks should have their circulation and respiration monitored constantly, with resuscitative equipment and personnel immediately available if needed. Do not exceed dosage recommendations. (See DOSAGE AND ADMINISTRATION.)

**Use in Ophthalmic Surgery:** With MARCAINE 0.75% for retrobulbar block, complete corneal anesthesia usually precedes onset of clinically acceptable external ocular muscle akinesia. Presence of akinesia alone determines readiness for surgery.

**Use in Dentistry:** Because of the long duration of anesthesia when MARCAINE 0.5% with epinephrine is used dentally, caution patients about inadvertent trauma to tongue, lips, and buccal mucosa; advise them not to chew solid foods or test the anesthetized area by biting or probing until anesthesia has worn off (up to 7 hours).

**Information for Patients:** When appropriate, inform them in advance of possible temporary loss of sensation and motor activity (usually in the lower body) following administration of caudal or epidural anesthesia, or other possible adverse occurrence noted in package insert.

**Clinically Significant Drug Interactions:** Administering local anesthetic solutions containing epinephrine or norepinephrine to patients receiving MAO inhibitors or tricyclic antidepressants may produce severe, prolonged hypertension. Thus concurrent use should generally be avoided; in situations when such therapy is necessary, careful monitoring is essential. Concurrent use of vasopressor and ergot-type oxytocic drugs may cause severe, persistent hypertension or cerebrovascular accident. Phenothiazines and butyrophenones may reduce or reverse epinephrine's pressor effect.

**Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Long-term studies in animals of most local anesthetics including bupivacaine have not been conducted. There is no evidence from human data that MARCAINE may be carcinogenic or mutagenic or that it impairs fertility.

**Pregnancy Category C:** Decreased pup survival in rats and an embryocidal effect in rabbits have been observed when bupivacaine was administered to either in doses comparable to 5 to 9 times the maximum recommended daily human dose (400 mg). There are no adequate and well-controlled studies in pregnant women of the drug's effect on fetal development, and potential fetal risk must be justified by potential benefit. This does not exclude use of MARCAINE at term for obstetric anesthesia or analgesia. (See Labor and Delivery.)

**Labor and Delivery:** SEE BOXED WARNING REGARDING OBSTETRIC USE OF 0.75% MARCAINE, and its contraindication in obstetric paracervical block. Local anesthetics cross the placenta rapidly and, when used for epidural, caudal, or pudendal block, can cause varying degrees of maternal, fetal, and neonatal toxicity. (See Pharmacokinetics in CLINICAL PHARMACOLOGY.) The incidence and degree of toxicity depend upon the procedure performed, and drug type, amount, and technique of administration. Adverse reactions in the parturient, fetus, and neonate involve alterations of the CNS, peripheral vascular tone, and cardiac function.

Maternal hypotension has resulted from regional anesthesia. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and left-side positioning will help prevent decrease in blood pressure. Fetal heart rate should be monitored continuously, preferably electronically. Epidural, caudal, or pudendal anesthesia may alter parturition through changes in uterine contractility or maternal expulsive efforts. Epidural anesthesia has been reported to prolong second-stage labor by removing the parturient's reflex urge to bear down, or by interference with motor function. Use of obstetric anesthesia may increase need for forceps assistance.

Some local anesthetic drugs may diminish muscle strength and tone for the first day or two of life. It is unreported with bupivacaine.

Of extreme importance: Avoid aortocaval compression of the gravid uterus during administration of regional block. To do this, maintain the parturient in the left lateral decubitus position, or place a blanket roll or sandbag beneath the right hip to displace the gravid uterus away from the great vessels.

**Nursing Mothers:** It is not known whether local anesthetics are excreted in human milk; because many drugs are, administer with caution.

**Pediatric Use:** Without further experience in children under 12, MARCAINE is not recommended for this group.

**ADVERSE REACTIONS:** A major cause of adverse reactions to amide-type local anesthetics is excessive plasma levels, possibly due to overdosage, unintentional intravascular injection, or slow metabolic degradation.

**Systemic:** The most common acute experiences, demanding immediate countermeasures, involve the CNS and cardiovascular systems. Adverse events are generally dose-related and due to high plasma levels which may result from overdosage, rapid absorption from the injection site, diminished tolerance, or unintentional intravascular injection of the solution. In addition to systemic dose-related toxicity, unintentional subarachnoid injection during performance of caudal or lumbar epidural block or nerve blocks near the vertebral column (especially in the head and neck region) may result in underventilation or apnea. Also, hypotension due to loss of sympathetic tone, and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia, may occur, leading to secondary cardiac arrest if untreated. Factors influencing plasma protein binding such as acidosis, systemic diseases which alter protein production or competition of other drugs for protein binding sites, may diminish individual tolerance.

**Central Nervous System:** Excitation and/or depression, restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly convulsions. Excitement may be transient, depression being the first manifestation of an adverse reaction. Drowsiness merging into unconsciousness and respiratory arrest may quickly follow. Other CNS effects may be nausea, vomiting, chills, pupillary constriction. Incidence of convulsions varies with the procedure used and total dose administered. In studies of epidural anesthesia, overt toxicity progressing to convulsions occurred in approximately 0.1% of procedures.

**Cardiovascular:** High doses of unintentional intravascular injection may lead to high plasma levels and related myocardial depression, decreased cardiac output, heart block, hypotension, bradycardia, ventricular arrhythmia including ventricular tachycardia and ventricular fibrillation, and cardiac arrest. (See WARNINGS, PRECAUTIONS, OVERDOSAGE.)

**Allergic:** Rare, and may occur as a result of sensitivity to the local anesthetic or to other formulation ingredients such as the antimicrobial preservative methylparaben contained in multiple-dose vials or sulfites in epinephrine-containing solutions. Possible reactions: urticaria, pruritus, erythema, angioneurotic edema (including laryngeal), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, perhaps anaphylactoid symptoms (including severe hypotension). Cross-sensitivity among members of the amide-type anesthetic group reported; value of sensitivity screening is unestablished.

**Neurologic:** Incidence of adverse reactions associated with use of such drugs may be related to the total dose administered, and dependent upon the particular drug use, route of administration, and the patient's physical status. Many effects may be related to technique, with or without the drug being contributory.

In performing caudal or lumbar epidural block, occasional unintentional penetration of the subarachnoid space by catheter or needle may occur. Subsequent adverse effects may depend partially on the amount of drug administered intrathecally and physiologic and physical effects of dural puncture. High spinals are characterized by leg paralysis, loss of consciousness, respiratory paralysis, and bradycardia. Effects following epidural or caudal anesthesia may include: spinal block of varying magnitude (including high or total spinal block); hypotension secondary to spinal block; urinary retention; fecal and urinary incontinence; loss of perineal sensation and sexual function; persistent anesthesia, paresthesia, weakness, paralysis of the lower extremities, and loss of sphincter control—all of which may show slow, incomplete, or no recovery; headache; backache; septic meningitis; meningism; slowing of labor; increased incidence of forceps delivery; cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid.

**OVERDOSAGE:** Acute emergency during therapeutic local anesthesia is generally related to high plasma levels or unintended subarachnoid injection of the solution. (See ADVERSE REACTIONS, WARNINGS, PRECAUTIONS.)

The first consideration in management is prevention, best accomplished by careful, constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each injection. At the first sign of change, administer oxygen. This measure may prevent convulsions if they have not already occurred. In systemic toxic reactions, as well as underventilation or apnea due to unintentional subarachnoid injection of drug solution, give immediate attention to establishing and maintaining a patent airway and controlled ventilation with 100% oxygen (the delivery system must permit instant positive airway pressure by mask). Endotracheal intubation may be indicated to meet the need for prolonged ventilatory support or if difficulty is encountered in the maintenance of a patent airway.

If necessary, use drugs to control convulsions. A 50-100 mg bolus I.V. injection of succinylcholine will paralyze the patient (without CNS or cardiovascular depression) and facilitate ventilation. A 5-10 mg I.V. bolus of diazepam, or 50-100 mg of thiopental, will permit ventilation and counteract CNS stimulation, but these drugs also depress CNS, respiratory and cardiac function, add to postictal depression, and may cause apnea. Intravenous barbiturates, anticonvulsant agents, or muscle relaxants should be administered only by those familiar with use. Immediately after institution of ventilatory measures, circulatory adequacy should be evaluated; supportive treatment may require administration of I.V. fluids and, when appropriate, a vasopressor dictated by the clinical situation (eg, ephedrine or epinephrine to enhance myocardial contractile force).

Recent clinical data from patients experiencing convulsions induced by local anesthetics demonstrated rapid development of hypoxia, hypercarbia, and acidosis; with bupivacaine, within a minute of onset. These observations suggest that $O_2$ consumption and $CO_2$ production are greatly increased during the convulsions and emphasize the importance of immediate ventilation with oxygen; if not treated effectively, convulsions and their complications plus myocardial depression from direct effects of the local anesthetic may result in cardiac arrhythmias, bradycardia, asystole, ventricular fibrillation, or cardiac arrest. Respiratory abnormalities including apnea may occur; underventilation or apnea due to unintentional subarachnoid injection of the solution may also lead to these signs and cardiac arrest if ventilatory support is not instituted. If cardiac arrest occurs, prolonged resuscitative effort may determine a successful outcome.

In treating systemic toxicity, maternal hypotension, or fetal bradycardia following regional block, avoid aortocaval compression by the gravid uterus. The supine position is dangerous, etc. (as in insert). (See Labor and Delivery in PRECAUTIONS.)

**Composition of Marcaine Solutions:** 0.25%—each mL contains 2.5 mg bupivacaine; 0.5%—each mL contains 5 mg bupivacaine; 0.75%—each mL contains 7.5 mg bupivacaine. All concentrations contain NaCl for isotonicity in Water for Injection.

In multiple-dose vials, each mL also contains 1 mg methylparaben. With epinephrine, each mL also contains 0.0091 mg epinephrine bitartrate, 0.5 mg sodium bisulfite, 0.001 mL monothioglycerol, 2 mg ascorbic acid, 0.0017 mL 60% sodium lactate, and 0.1 mg edetate calcium disodium.

1. Ostheimer GW: Neurobehavioral effects of local anesthesia and fetal resuscitation. *Reg Anesth* 1981;6:136-145.
2. Naulty JS, Ostheimer G, Datta S, et al: Bupivacaine in breast milk following epidural anesthesia for vaginal delivery. Presented as a scientific poster at the Annual Meeting of the American Society of Regional Anesthesia, Lake Buena Vista, FL, March 23-27, 1983.

Winthrop-Breon

**WINTHROP-BREON LABORATORIES**
90 Park Avenue, New York, NY 10016

# High-Frequency Oscillatory Ventilation and Pulmonary Extravascular Water

Masanori Tamura, MD, Toshio Kawano, MD, Ingrid Fitz-James, MD, and A. Charles Bryan, MB, BS, PhD

TAMURA M, KAWANO T, FITZ-JAMES I, BRYAN AC. High-frequency oscillatory ventilation and pulmonary extravascular water. Anesth Analg 1985;24:1041–6.

*The lungs of anesthetized rabbits were embolized by intravenous injection of 75 mg/kg of starch particles in divided doses. One group received high-frequency oscillatory ventilation (HFOV) at a rate of 15 Hz. Both groups were ventilated with an* $F_{I_{O_2}}$ *of 1.0. After 3 hr of ventilation, the animals were sacrificed, and the extravascular lung water (EVLW) was determined gravimetrically. With conventional mechanical ventilation (CMV), the EVLW/body weight ratio was 4.1 ± 1.4 g/kg (mean ± SD) and was significantly higher than the ratio of 2.8 ± 0.6 in animals given HFOV* ($P < 0.05$)*. In a second series of animals, 20 μCi of* $^{125}$*I-labeled bovine albumin was injected intravenously prior to embolization and followed by the same two types of ventilation. After the rabbits were sacrificed, the lungs were lavaged with 0.9 N saline, and the radioactivity of the fluid was measured to determine the protein leak. After CMV, 2.76 ± 2.05% of the injected radioactivity was recovered from the fluid, significantly higher* ($P < 0.01$) *than the amount of radioactivity recovered after HFOV, 0.3 ± 0.28%. There also was significantly more labeled protein in the lung tissue that had been on CMV. We conclude that in this model of pulmonary edema, HFOV significantly reduces both the amount of fluid and protein leaking into the lung.*

Key Words: LUNG—edema. EMBOLISM—starch. VENTILATION—artificial, high frequency.

There have been a number of studies on the effect of high-frequency oscillatory ventilation (HFOV) on pulmonary lymphatic flow that have had conflicting results (1–4). The more general question of what HFOV does to the Starling balance of forces that govern fluid movement across the lungs does not appear to have been studied. With the very different pressure–time profile on HFOV compared to conventional mechanical ventilation (CMV), differences in fluid flux across the lung might be expected. Kudoh (5) has shown that a mechanically ventilated lung develops more pulmonary edema than a contralateral lung held statically inflated. HFOV is essentially static inflation with a small superimposed pressure fluctuation. We have, therefore, compared the effects of HFOV and CMV on a model of pulmonary edema created by starch embolization of the lung.

## Methods

Adult male New Zealand white rabbits (3.3 ± 0.4 kg) were premedicated with acepromazine (0.3 mg/kg intramuscularly). Anesthesia was induced with ketamine (3.5 mg/kg intravenously) and thiopental (7 mg/kg intravenously). A tracheostomy was performed and a 3.5-mm endotracheal tube secured in place. A control group (five animals) was immediately sacrificed with KCl intravenously. The remaining animals were paralyzed with pancuronium bromide (0.3 mg/kg intravenously) and assigned to either CMV or HFOV. Anesthesia and paralysis were maintained with intermittent doses of ketamine and pancuronium bromide. A catheter was inserted into the femoral artery, and arterial blood samples were drawn every 30 min for blood gas analysis. Between samples, the catheter was used to measure blood pressure with a pressure transducer (HP 267BC). Fluid balance was maintained by the infusion of 0.9 N saline with 5% glucose at a rate of 9 ml $\cdot$ kg$^{-1}$ $\cdot$ hr$^{-1}$. Body temperature was maintained with a servocontrolled radiant heater (Air Shields). The ECG, blood pressure, and airway pressure were recorded on a polygraph (Hewlett-Packard). Total plasma proteins were measured at

---

Supported by Medical Research Council Grant #MA 6342.
Received from the Department of Respiratory Physiology, Research Institute, Hospital for Sick Children, Toronto, Canada.

Address correspondence to Dr. Bryan, Respiratory Physiology, Hospital for Sick Children, 555 University Avenue, Toronto M5G 1X8, Canada.

© 1985 by the International Anesthesia Research Society

the beginning and the end of the experiment with a refractometer (American Optical).

Conventional mechanical ventilation was provided by a Bournes BP 200 infant ventilator. The initial settings were $F_{I_{O_2}}$, 1.0; peak pressure, 20 cm $H_2O$; positive end-expiratory pressure, 2 cm $H_2O$; rate, 30 breaths/min; inspiratory/expiratory ratio, 1:3. The mean pressure on these settings was approximately 6 cm $H_2O$. During the last hour of the study, ventilator pressures had to be increased to maintain normal blood–gas tensions.

High-frequency oscillatory ventilation was provided by a pump and circuit as described previously (6,7). The rate was 15 Hz, the volume displacement 1–2 ml/kg, and the mean airway pressure was measured at the junction of the circuit connector and the endotracheal tube. Because of reports of gas trapping on HFOV (8,9), we also intermittently occluded the airway to obtain the alveolar pressure.

After a brief period of stabilization on one or the other mode of ventilation, the lungs were embolized with an intravenous injection of a suspension of potato starch with a particle size of 63–74 μm. A total dose of 75 mg/kg was given in divided doses, producing substantial pulmonary edema with a relatively low mortality. The initial dose was 25 mg/kg, followed by four additional injections of 12.5 mg/kg at 30-min intervals. Four hr after the initial embolization, the animals were sacrificed by intravenous injection of KCl.

Three different groups of animals were used: one to measure extravascular lung water, one to measure pulmonary protein leak, and one for pathological examination.

### *Measurement of Lung Water*

After sacrifice, the trachea was clamped, the lungs removed, and lung water measured by the gravimetric technique described by Pearce et al. (10). The lungs were weighed and then homogenized in distilled water. An aliquot of the homogenate was centrifuged at 8000 g for 30 min, and the hemoglobin in the supernatant was measured. The rest of the homogenate was weighed and evaporated to a constant weight in an oven at 60°C. From these measurements, wet and dry weights, corrected for pulmonary blood volume, were obtained, from which pulmonary extravascular water was calculated. These measurements were made on the five control animals, the 12 rabbits embolized during CMV, and the 12 rabbits embolized during HFOV.

### *Measurements of Protein Leak*

In the second series of rabbits, an identical embolization/ventilation protocol was followed, but 1 hr before the first starch injection, 20 μCi of $^{125}I$ bovine serum albumin was injected into the jugular vein. Arterial blood samples were taken every 15 min and the activity measured in a well counter (Beckman) to obtain the clearance rate of albumin from the vascular system. After the rabbits were sacrificed, the lungs were lavaged with 20 ml/kg of 0.9 N saline flushed in and out three times, followed by five more lavages. The radioactivity of the pooled lavage fluid was measured in a well counter to obtain the alveolar protein leak. The lung was then homogenized and its activity measured to obtain the protein leak into the tissue (after correction for the radioactivity in the pulmonary blood volume (11,12)). These measurements were made in seven rabbits embolized during CMV and seven rabbits embolized during HFOV.

### *Pathological Examination*

In the third series, after an identical embolization/ventilation protocol, the lungs were removed for pathological examination immediately after sacrifice. A piece of the right lower lobe was fixed in glutaraldehyde for electron microscopy. The remainder of the right lung was fixed in Bouin's solution and the left lung in formalin for light microscopy. Three rabbits embolized during CMV and three embolized during HFOV were studied.

### *Statistical Analysis*

Analysis was done using the Student's unpaired *t*-test. All results are presented at mean ± 1 SD. Significance was assumed to be $P < 0.05$.

## Results

### *Gas Exchange*

Arterial blood–gas tensions and the mean airway pressures after embolization on the two forms of ventilation are presented in Table 1. During HFOV, homeostasis of blood–gas tensions was maintained throughout the experiment. In contrast, during CMV there was a progressive decrease in arterial oxygen tension that necessitated increasing the ventilator pressures during the last hour to avoid hypoxia. Only in the last hour were the blood–gas tensions and pH significantly different between animals managed on CMV and HFOV.

Table 1. Time Course of Arterial Blood–Gas Tensions and Mean Airway Pressure in Series 1 and 2

| | 0 | 0.5 hr | 1 hr | 2 hr | 3 hr | End |
|---|---|---|---|---|---|---|
| pH | | | | | | |
| CMV | 7.47 ± 0.06 | 7.39 ± 0.10 | 7.40 ± 0.08 | 7.37 ± 0.11 | 7.27 ± 0.12 | 7.19 ± 0.12 |
| HFOV | 7.43 ± 0.08 | 7.42 ± 0.08 | 7.39 ± 0.07 | 7.33 ± 0.08 | 7.34 ± 0.07 | 7.32 ± 0.11[*] |
| $Pa_{O_2}$, | | | | | | |
| CMV | 410 ± 32 | 370 ± 74 | 392 ± 96 | 839 ± 135 | 292 ± 141 | 207 ± 165 |
| HFOV | 393 ± 73 | 396 ± 55 | 414 ± 57 | 372 ± 83 | 394 ± 94 | 391 ± 90 |
| $Pa_{CO_2}$ (mm Hg) | | | | | | |
| CMV | 31 ± 7 | 33 ± 8 | 32 ± 8 | 34 ± 9 | 40 ± 10 | 42 ± 12 |
| HFOV | 34 ± 5 | 32 ± 5 | 34 ± 4 | 36 ± 6 | 35 ± 4 | 33 ± 7[*] |
| MAP (cm $H_2O$) | | | | | | |
| CMV | 6.1 ± 0.3 | 6.1 ± 0.3 | 6.2 ± 0.4 | 6.3 ± 0.7 | 6.4 ± 0.7 | 7.1 ± 1.4 |
| HFOV | 5.6 ± 0.6 | 5.6 ± 0.5 | 5.6 ± 0.5 | 5.7 ± 0.5 | 5.8 ± 0.7 | 5.8 ± 0.7[*] |

Values are means ± SD; $n = 19$. Abbreviations: MAP, mean airway pressure; End, at the time of sacrifice; CMV, conventional mechanical ventilation; HFOV, high-frequency oscillatory ventilation.

[*]Significantly different from corresponding CMV value ($P < 0.05$).

Table 2. Extravascular Lung Water

| | Number of rabbits | EVLW/BW (g/kg) | EVLW/DLT (g/g) |
|---|---|---|---|
| Control | 5 | 1.8 ± 0.6 | 3.5 ± 0.6 |
| CMV | 12 | 4.1 ± 1.4 | 7.9 ± 2.6 |
| HFOV | 12 | 2.8 ± 0.6[*] | 5.4 ± 1.2[*] |

Values are means ± SD. Abbreviations: EVLW, extravascular lung water; DLT, corrected dry lung tissue weight; BW, body weight.

[*]Significantly different corresponding CMV value ($P < 0.05$).

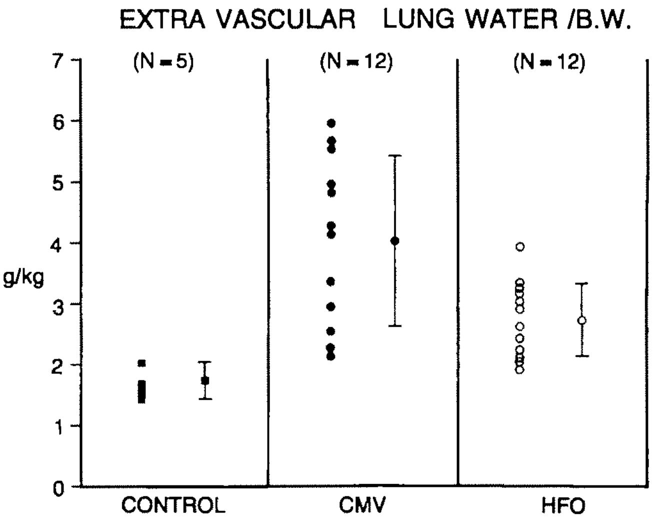


Figure 1. Comparative extravascular lung water values during CMV and HFO, mean ± SD are represented. Healthy rabbits (■), starch embolization treated on CMV (●), starch embolization treated on HFO (○). Extravascular lung water/body weight is significantly lower on HFO than CMV ($P < 0.05$).

## Lung Volume

There was no significant difference between the mean airway pressure and the pressure measured during airway occlusion (alveolar pressure) during HFOV; therefore there was no evidence of gas trapping.

## Extravascular Lung Water

The extravascular lung water results are presented in Table 2 normalized to both body weight and to dry lung tissue weight. After embolization there was a significant increase in lung water on both forms of ventilation, but the lung water after CMV was significantly higher ($P < 0.05$) than after HFOV (Fig. 1).

## Protein Leak

The percentages of the injected albumin that leaked into the lung are presented in Table 3. The alveolar leak was highly significantly greater ($P < 0.01$) during CMV (2.75 ± 2.05%) than during HFOV (0.3 ± 0.28%) (Fig. 2). The albumin leak into lung tissue was also significantly greater ($P < 0.05$) during CMV (Fig. 3). The half-time clearance of albumin from the vascular space was not significantly different between the two modes of ventilation prior to embolization. After embolization, there was no significant change in the half-time during HFOV. In contrast, during CMV the half-time was significantly faster ($P < 0.01$) than either preembolization or postembolization during HFOV.

## Pathology

Light microscopy showed widespread starch emboli, moderate interstitial and alveolar edema, and patchy pneumonitis. Electron microscopy showed focal swelling of type I cells, but otherwise intact epithelium. There were intraalveolar fibrin strands and endothelial bleb formation. There was no detectable

Table 3. $^{125}$I-Albumin Leak from Half-Time Clearance from Blood

| | Number of rabbits | Leak in alveolus | Leak in tissue | $^{125}$I Half-time clearance | |
|---|---|---|---|---|---|
| | | | | Before starch | After starch |
| CMV | 7 | 2.76 ± 2.05 | 1.12 ± 0.41 | 568 ± 241 | 170 ± 79 |
| HFO | 7 | 0.30 ± 0.28$^b$ | 0.42 ± 0.41$^a$ | 631 ± 460 | 659 ± 247$^b$ |

Values are means ± SD.
Significantly different corresponding CMV value, $^aP < 0.05$; $^bP < 0.01$.

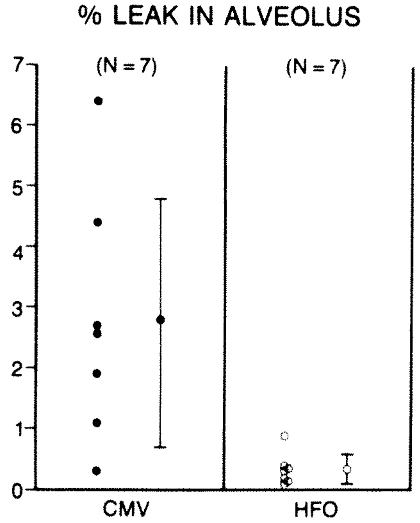


Figure 2. Comparison of $^{125}$I-albumin associated with alveolar wash mean % ± SD of initial $^{125}$I-albumin dose injected through the external jugular vein that was recovered by alveolar wash. Rabbits on CMV and HFOV are indicated by ● and ○, respectively. Percent leak in alveolus is significantly lower on HFOV ($P < 0.01$).

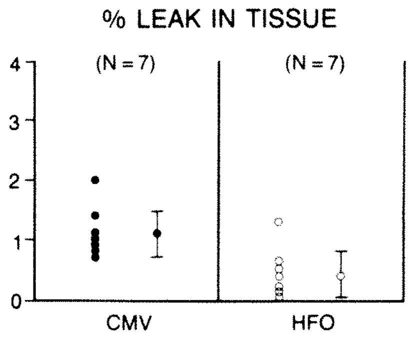


Figure 3. Comparison of $^{125}$I-albumin associated with lung tissue mean % ± SD of initial $^{125}$I-albumin dose injected through the external jugular vein that was associated with the lung tissue. Rabbits on CMV and HFOV are indicated by ● and ○, respectively. Percent leak associated with tissue is significantly lower on HFOV ($P < 0.05$).

pathological difference between animals after CMV and HFOV.

## Discussion

The association of pulmonary edema with pulmonary embolism has been widely observed, but the mechanism is controversial (13–16). The leak appears to be due to a number of factors (17–18) including mediator release from granulocytes and platelets, direct injury to the capilliary endothelium, and local increase in intravascular pressure due to starch particles and fibrin aggregates.

In this study, after starch embolization, there was less extravascular lung water and less protein leakage into the lung during HFOV than during CMV. The reason for this difference is not clear, but it could be due to differences in pulmonary lymph flow. Warren and Drinker (19) suggested that phasic lung inflation was important for normal pulmonary lymphatic flow. There are no large phasic movements of the lung during HFOV, and several groups have studied the effect of this mode of ventilation on pulmonary lymph flow. However, the results are conflicting. Mitzner et al. and Raj et al. (2,3) found a small decrease in lymph flow during HFOV but no increase in extravascular lung water. Martin et al. (4) found an increase in lymph flow with a small increase in lung water. Jefferies et al. (1) found no change in either lymph flow or lung water during HFOV. These conflicting results are probably due to variability of methodologies, i.e., excised lungs, open or closed chest, or the use of sheep or dogs. Given this variability, we can draw no conclusion about the role of HFOV on lymphatic flow.

It is possible that HFOV affects lung water by altering the Starling balance of forces governing transvascular fluid flux, namely:

$$Q = K\,(Pmv - Pis) - K\sigma\,(\pi mv - \pi is)$$

where $Q$ is the filtration rate, $P$ the hydrostatic pressure, $\pi$ the osmotic pressure, $K$ the conductance of the barrier, $\sigma$ the reflection coefficient, and $mv$ and $is$ the microvascular and interstitial compartments, respectively.

The conductance, $K$, is a function of both surface area and pore size. One would predict that as the mean airway pressure was the same, the animals on CMV who had more edema would be less compliant and have a lower lung volume and less surface area. However, during CMV, the lung is cycled between a large and a small lung volume, whereas during HFOV, the lung volume is relatively fixed. Therefore, it is difficult to draw conclusions about the surface area.

There was no obvious difference in anatomical pore size, nor was there difference in the degree of endothelial injury, and the epithelium appeared intact by both light and electron microscopy during CMV and HFOV. The similarity of the static appearance, however, does not exclude dynamic differences. Egan (20) suggested that alveolar pore size was a function of transpulmonary pressure, the pores getting larger with lung inflation and not immediately getting smaller on deflation. However, in a subsequent study he showed that opening pores in the normally tight epithelial junctions required gross local overdistention (21). Staub (22) also showed that the rate of peribronchial fluid cuff formation was faster at high distending pressures. It is therefore possible that the leak was greater during CMV because the peak pressure was higher than it was during HFOV. The mean airway pressures during the two forms of ventilation were similar until the blood-gas tensions began to deteriorate towards the end of the experiment. Recently the accuracy of the mean airway pressure measured during HFOV has been questioned by Saari et al. and Simon et al. (8,9) who have found gas trapping during HFOV. In the present experiments, there was no evidence of gas trapping; the measured mean airway pressure was similar to the occlusion (alveolar) pressure.

We were unable to measure pulmonary intravascular pressures in the rabbits, but in preliminary experiments in dogs there was stepwise increase in pulmonary artery pressure with each starch injection and no significant difference in either pressure or cardiac output between the two forms of ventilation. Therefore, the average pulmonary vascular pressure did not differ. Despite this, the very different patterns of lung inflation observed during CMV and HFOV must have a considerable effect on pulmonary hemodynamics. Jansen et al. (23) have shown, using dogs on mechanical ventilation, that during expiration the cardiac output is 40% higher than it is during peak inspiration. In addition, Smith et al. (24) have shown that the relationship between airway pressure and pulmonary vascular impedance is exponential, impedance rising very steeply as airway pressure is increased. These changes would be reflected in cyclical changes in pulmonary microvascular pressure during CMV that would be small or absent during HFOV.

Changes in the interstitial pressure (*Pis*) may also be a significant factor in fluid accumulation on CMV. Howell et al. (25) showed that lung inflation causes a decrease in interstitial pressure around the extraalveolar vessels and an increase around the alveolar vessels. As a result of these pressure changes, Goldberg (26) has suggested that lung inflation may cause a shift of fluid from the interstitial space around the alveolar vessels to the interstitial space around the extraalveolar vessels. By pumping the fluid out of the alveolar interstitial space, the local interstitial pressure would remain low, allowing for further accumulation of fluid in that space. This transport mechanism would not be present with the relatively fixed lung volume during HFOV. Under these circumstances, fluid would accumulate in the alveolar interstitial space, increasing the interstitial pressure, thus limiting further leakage.

We conclude that HFOV reduces the rate of edema formation and protein leak by acting on either one or several factors regulating lung fluid balance. However, it must be stressed that these conclusions apply to pulmonary edema in rabbits subjected to starch embolization. Their relevance to either high-pressure or -permeability edema in humans is questionable.

## References

1. Jefferies AL, Hamilton P, O'Brodovich HM. Effect of high frequency oscillation on lung lymph flow. J Appl Physiol 1983;55:1373–8.
2. Mitzner W, Sylvester JT, Permutt S. Effects of ventilation on lymph flow from the isolated perfused lamb lung (abstract). Physiologist 1981;24:54.
3. Raj JU, Goldberg RB, Bland RD. Vibratory ventilation decreases filtration of fluid in the lungs of newborn lambs. Circ Res 1983;53:456–63.
4. Martin D, Rehder K, Parker JC, Taylor AE. High frequency ventilation: lymph flow, lymph protein flux, and lung water. J Appl Physiol 1984;57:240–5.
5. Kudoh I. Effect of mechanical ventilation on lung water volume in dogs. Crit Care Med 1984;12:443–6.
6. Hamilton PP, Onayemi A, Smyth JA, Gillan JE, Cutz E, Froese AB, Bryan AC. Comparison of conventional and high frequency ventilation: oxygenation and lung pathology. J Appl Physiol 1983;55:131–8.
7. Kolton M, Cattran CB, Kent G, Volgyesi G, Froese AB, Bryan AC. Oxygenation during high frequency ventilation compared with conventional mechanical ventilation in two models of lung injury. Anesth Analg 1982;61:323–32.
8. Saari AF, Rossing TH, Solway J, Drazen JM. Lung inflation during high frequency ventilation. Am Rev Respir Dis 1984;129:333–6.
9. Simon BA, Weinmann GG, Mitzner W. Mean airway pressure and alveolar pressure during high frequency ventilation. J Appl Physiol 1984;57:1069–78.
10. Pearce ML, Yamashita J, Beazell J. Measurement of pulmonary edema. Circ Res 1965;16:482–8.
11. Anderson RR, Holliday RL, Dreidger AA, Lefcoe M, Reid B, Sibbald WJ. Documentation of pulmonary capillary permeability in the adult respiratory distress syndrome accompanying human sepsis. Am Rev Respir Dis 1979;119:869–77.
12. Jobe A, Ikegami M, Jacobs H, Jones S, Conaway D. Permeability of premature lamb lungs to protein and the effect of surfactant on that permeability. J Appl Physiol 1983;55:169–76.
13. Rosenow EC, Osmundson PJ, Brown ML. Pulmonary embolism. Mayo Clinic Proc 1981;56:161–8.
14. Saldeen T. The microembolism syndrome. Micro Res 1976;11:227–59.

15. Johnson A, Malik AB. Effects of different size microemboli on lung fluid and protein exchange. J Appl Physiol 1981;51:461–70.
16. Malik AB, VanDerZee H. Mechanism of pulmonary edema induced by microembolization in dogs. Circ Res 1979;42:72–8.
17. Johnson A, Malik AB. Effect of granulocytopenia on extravascular lung water content after microembolization. Am Rev Respir Dis 1980;122:561–6.
18. Flink JR, Pitt BR, Hammond GL, Gillis CN. Selective effects of microembolization on pulmonary removal of biogenic amines. J Appl Physiol 1982;52:421–27.
19. Warren MF, Drinker CK. The flow of lymph from the lungs of the dog. Am J Physiol 1942;136:207–21.
20. Egan EA. Response of alveolar epithelial solute permeability to changes in lung inflation. J Appl Physiol 1980;49:1032–6.
21. Egan EA. Lung inflation, lung solute permeability and alveolar edema. J Appl Physiol 1982;53:122–5.
22. Staub NC. Pathways for fluid and solute fluxes in pulmonary edema. In: Fishman AP, Renkin EM, eds. Pulmonary edema. Bethesda, MD: American Physiological Society, 1979:113–24.
23. Jansen JRC, Schreuder JJ, Bogaard JM, vanRooyen W, Versprille A. Thermodilution technique for measurement of cardiac output during artificial ventilation. J Appl Physiol 1981;51:584–91.
24. Smith PK, Tyson GS, Hammon JW, Olsen CO, Hopkins RA, Maier GW, Sabiston DC, Rankin JS. Cardiovascular effects of ventilation with positive expiratory airway pressure. Ann Surg 1982;195:121–30.
25. Howell KBL, Permutt S, Proctor DF, Riley RL. Effect of inflation of the lung on different parts of pulmonary vascular bed. J Appl Physiol 1961;16:71–6.
26. Goldberg HS. Effect of lung volume history on rate of edema formation in isolated canine lobe. J Appl Physiol 1978;45:880–4.

# Inactivation of Atracurium in Human and Rat Plasma

Vladimir Nigrovic, MD, Jyoti B. Pandya, MD, Melissa Auen, BS, and Aron Wajskol, MD

NIGROVIC V, PANDYA JB, AUEN M, WAJSKOL A. Inactivation of atracurium in human and rat plasma. Anesth Analg 1985;64:1047–52.

*The contribution of enzyme-catalyzed hydrolysis to inactivation of atracurium in human and rat plasma was determined in vitro by inhibiting the enzyme carboxylesterase with triorthotolyl phosphate. The inhibitor was removed by centrifugation and aspiration. Atracurium was then added to both the control and the inhibited plasma samples, and all samples were incubated at 37°C for 45 min. The amount of atracurium present in aliquots of plasma was determined using a bioassay technique in anesthetized rats. Inactivation of atracurium proceeded rapidly in control rat plasma but was markedly slowed in samples treated with the inhibitor of carboxylesterase. In contrast, the inactivation was slow in control human plasma, and inhibition of carboxylesterase produced only marginal, if any, effects. We conclude that the inactivation of atracurium proceeds, in part, by enzyme-catalyzed ester hydrolysis. In species with high enzyme activity in plasma, e.g., the rat, enzyme-catalyzed hydrolysis is clearly evident. In humans, the level of enzyme activity is low and the contribution of enzyme-catalyzed inactivation is less manifest. By exclusion, Hofmann elimination or other reactions probably represent the major inactivation pathway in humans.*

Key Words: NEUROMUSCULAR RELAXANTS—atracurium. BIOTRANSFORMATION—enzymatic hydrolysis, carboxylesterase. BIOTRANSFORMATION—Hofmann elimination.

Atracurium, a new nondepolarizing muscle relaxant, offers the advantage of intermediate duration of action. This property is ascribed to chemical characteristics deliberately built into the molecule (1–10). Structurally, atracurium can be represented either as a coiled molecule, in order to highlight its resemblance to *d*-tubocurarine or metocurine (11), or as a linear, dumbbell-like molecule consisting of an aliphatic chain interposed between two bulky, quaternary nitrogen groups (1). The latter presentation is customarily utilized to point out the bis-quaternary structure characteristic of a nondepolarizing muscle relaxant. Separation of the two cationic groups by the splitting of the aliphatic chain leads to inactivation. By design (1), the break can occur on either end of the chain at the bond between the terminal carbon atom and the quaternary nitrogen. This reaction—termed Hofmann elimination—is temperature dependent and facilitated by nucleophiles, e.g., hydroxyl groups. In addition to Hofmann elimination, hydrolysis at either one of the ester sites within the chain was also postulated to disrupt the bis-quaternary structure (3,4). Thus destruction of the chain by either Hofmann elimination or ester hydrolysis leads to inactivation of atracurium. Relative contribution of each pathway to the overall inactivation of atracurium is not known.

In previous studies in humans, concentrations of atracurium and its metabolites were measured in plasma (9,12–14). Excretion of the parent drug and the metabolites in the bile and urine of cats has also been measured (4). These data, however, cannot be used to resolve the issue of the relative contributions of Hofmann elimination and ester hydrolysis in the inactivation of atracurium. The reason is that, while both processes can occur as either the first or the second step in the degradation of atracurium, only the first step is required for pharmacologic inactivation.

An opportunity to resolve this question directly was offered by the suggestion of Merrett et al. (3) that nonspecific plasma esterases catalyze hydrolysis of atracurium. We have tested this suggestion experimentally in rats (15). The enzyme carboxylic ester hydrolase (carboxylesterase) was inhibited by treating the rats with an organophosphorous compound, triorthotolyl phosphate (TOTP). We reasoned that by decreasing or eliminating the enzyme-catalyzed inactivation, we could obtain an estimate of the contribution of the remaining, spontaneous inactivation via Hofmann elimination. Because in treated animals duration of action of atracurium was markedly prolonged and the recovery rate slowed, we concluded that Hofmann elimination does not determine the duration of action of atracurium in rats.

Results obtained in rats may or may not be indic-

---

Received from the Departments of Anesthesiology and Pharmacology, Medical College of Ohio, Toledo, Ohio. Accepted for publication April 2, 1985.

Address correspondence to Dr. Nigrovic, Department of Anesthesiology, Medical College of Ohio, C.S. #10008, Toledo, OH 43699.

© 1985 by the International Anesthesia Research Society

ative of the inactivation pathways of atracurium in humans. Because application of the same experimental method was not permissible in humans, we decided to study the rate of inactivation of atracurium during incubation in untreated human plasma or in human plasma previously treated in vitro with an inhibitor of carboxylesterase. Selection of TOTP as the inhibitor was predicated on the data of Silver and Murphy (16).

Our experimental design was based on the following premise: If the inactivation of atracurium proceeds along two pathways, then the inhibition of one pathway, viz., the enzyme-catalyzed hydrolysis, should slow the process. The fractional amount of atracurium left over at the end of incubation should be proportional to the relative magnitude of the inhibited pathway. The larger the contribution of the enzyme-catalyzed inactivation, the larger will be the difference in the amount of atracurium remaining after incubation in TOTP-treated plasma as compared to the amount remaining in uninhibited (control) samples.

The validity of our hypothesis and of the experimental design was first established using rat plasma because the rate of inactivation via enzyme-catalyzed hydrolysis was known to be high in this species (15). Preliminary results of this study have been published (17).

## Methods

Heparinized blood from two healthy male volunteers (the authors) was rapidly centrifuged, and the separated plasma was stored at −70°C in aliquots of 4.5 ml until utilized (within 10 days). Rat plasma was similarly treated except that samples from several animals were pooled. Plasma samples from either source were thawed in Erlenmeyer flasks at 37°C in an atmosphere of humidified mixture of 5% carbon dioxide in oxygen and incubated under the same conditions with or without the addition of TOTP (1 ml to 4.5 ml of plasma). At the end of 60 min of incubation, TOTP-treated samples were centrifuged, and the supernatant plasma was aspirated. Collected plasma was then incubated for an additional 30 min to reestablish the partial pressure of carbon dioxide and, hence, the pH. Five milligrams of atracurium (0.5 ml of a commercial solution containing 10 mg of atracurium per ml) was added to randomly selected plasma samples without interrupting the incubation. The time of addition of atracurium was taken as zero time and immediately thereafter two aliquots were withdrawn from each sample: the first for the bioassay of the amount of atracurium present and the other for determination of pH and the partial pressure of carbon dioxide. After 45 min of continued incubation, two additional aliquots from each sample were obtained for the same purpose. Determinations of the amount of atracurium present in each of the plasma aliquots, collected either at the start or at the end of incubation, were always performed in the same rat. The aliquots were injected intravenously (1.2 ml·kg$^{-1}$) immediately after collection. The dose of atracurium injected with the first aliquot, collected immediately after the addition of atracurium (zero incubation time), was 1.2 mg·kg$^{-1}$.

Male rats were anesthetized by an intraperitoneal injection of pentobarbital (60 mg·kg$^{-1}$). During the procedure the rat was positioned on a heated blanket to maintain rectal temperature at 37°C. Ventilation with room air was established using a rodent ventilator and a short piece of plastic tubing as a tracheostomy cannula. Arterial pressure was obtained using a pressure transducer and a catheter inserted in the right femoral artery. The adjacent vein was cannulated for infusion of physiologic saline (0.9% NaCl at 10.0 ml·kg$^{-1}$·hr$^{-1}$) and injection of drugs. Contractions of the left gastrocnemius muscle were recorded using a force transducer (Grass FT 10) connected via a thread to the free end of the severed Achilles tendon. Preload was adjusted to optimize the contractions. The proximal end of the muscle was stabilized using a pin inserted into the femur. The left sciatic nerve was transected and its distal stump placed on a pair of platinum electrodes. Stimulation was performed using a Grass SS 88 stimulator and a stimulus isolation unit (Grass SIU 7) supplying a supramaximal square-wave stimulus of 0.2 msec duration at 0.2 Hz. The wounds were covered with mineral oil to prevent dessication. At the end of the experiment a sample of arterial blood was obtained for gas analysis.

The outputs from the pressure and force transducers were recorded on a polygraph. The height of the twitch produced by muscle contraction was used to quantify and evaluate the following parameters: 1) onset of the maximal relaxation, defined as the time in seconds between the injection of an aliquot containing atracurium and the maximal twitch suppression; 2) duration of action, defined as time in seconds between the injection of an aliquot containing atracurium and the recovery of contractions to 10% of the control value; 3) residual twitch activity, defined as the smallest mechanical response remaining after the injection of atracurium and expressed as percent of the preinjection value; and 4) rate of recovery, calculated as the slope of the straight line connecting the peaks of the mechanical responses during the recovery and expressed as percent of the mechanical response recovered per minute.

Because our experimental design entails a bioassay

Table 1. Dose–Response Relationship for Atracurium in Rats ($n = 4$)

| | Dose of atracurium (mg·kg$^{-1}$) intravenously | | | | | |
|---|---|---|---|---|---|---|
| | 0.3 | 0.6 | 1.2 | 2.4 | Pooled SEM | $P$[a] |
| Onset of maximal relaxation (sec) | 60.8 | 65.3 | 43.4 | 34.3 | 4.1 | < 0.001 |
| Duration to 10% twitch recovery (sec) | [b] | [c] | 212 | 386 | 23 | |
| Residual twitch activity (% of control) | 38.0 | 22.4 | 1.84 | 1.05 | 4.6 | < 0.001 |
| Recovery rate (% recovered per min) | 30.2 | 37.6 | 30.5 | 26.5 | 3.6 | 0.2 |
| Body weight (g) | 261 | 280 | 302 | 268 | 12.0 | NS |
| Arterial pH[d] | 7.42 | 7.37 | 7.36 | 7.40 | 0.02 | NS |
| Arterial $P_{CO_2}$ (torr)[d] | 29 | 29 | 33 | 31 | 1.9 | NS |

Four rats were tested in each group and each dose was administered twice to a single animal. See text for details.

[a] Probability that the differences in responses produced by different doses of atracurium may be ascribed to a chance observation. NS, not significant.

[b] Residual twitch activity remained above 10% of the preinjection (control) value in seven out of eight observations.

[c] Residual twitch activity was decreased below 10% of the preinjection (control) value in four out of eight observations (mean duration of maximal relaxation was 92 sec).

[d] Arterial blood was sampled before termination of the experiment.

of the amount of atracurium present in plasma after different incubation periods, we first studied the relationship between various doses of atracurium and the corresponding pharmacologic responses in the test animal (dose–response study). A comparison of responses produced by known amounts of atracurium with those produced by injection of plasma aliquots with unknown amounts would permit us to estimate the amount of atracurium present in plasma aliquots. Skeletal muscle relaxation produced by four doses of atracurium (0.3, 0.6, 1.2, and 2.4 mg·kg$^{-1}$ intravenously) was studied in eight rats. The doses were arranged in two pairs (0.3 and 1.2; 0.6 and 2.4 mg·kg$^{-1}$) and each pair was administered to four rats. In one half of the animals, injection of a larger dose preceded the injection of a smaller dose by 45 min. In the other half, the order of injections was reversed. Two additional points had to be clarified in preliminary experiments: was the relaxation produced by the second intravenous administration of atracurium into the same animal influenced by the preceding injection; and was the separation of TOTP from plasma complete or could residues of TOTP remaining in and injected with aliquots of plasma alter the response to simultaneously or subsequently administered atracurium? To answer the first question, five animals were treated with two intravenous injections of atracurium (1.2 mg·kg$^{-1}$) at a 45-min interval, and the pharmacologic responses were compared. To answer the second question, aliquots (1.2 ml·kg$^{-1}$) of control or TOTP-treated human plasma were injected intravenously 15 min prior to the injection of atracurium (1.2 mg·kg$^{-1}$).

Statistical analysis was performed using a 2 × 2 factorial approach (18). The two factors and their levels were duration of incubation (either 0 or 45 min) and enzyme activity (either control or inhibited by TOTP treatment). Because the number of observations was the same in each of the four experimental groups, the design was optimal to determine an interaction between the duration of incubation and the level of enzyme activity. Significant interaction, if detected, would imply that the inactivation of atracurium during incubation in plasma was dependent on the level of enzyme activity. Thus assuming a measurable contribution of enzyme-catalyzed hydrolysis in the overall inactivation of atracurium, one would expect to find the changes ascribable to the two factors and to their interaction to be unlikely to have been observed by chance ($P < 0.05$).

## Results

Statistical analysis of the two preliminary experiments showed that there was no difference in responses between the two administrations of atracurium and that muscle paralysis produced by atracurium was not influenced by the preceding injections of either the control or the TOTP-treated plasma (data not presented).

The results of the dose–response study are presented in Table 1. As in the preliminary experiment with equal doses of atracurium, the sequence of injections of variable doses did not influence the measured parameters of muscle paralysis. All observations obtained using identical doses were, therefore, pooled. The results show that as the dose of atracurium was increased, residual twitch activity decreased and the time interval to the onset of the maximal relaxation shortened. Duration of action could not be measured reliably for the two lower doses of atracurium because the residual twitch activity remained above 10% of the preinjection (control) level; the two higher doses produced a progressively increased du-

Table 2. Incubation of Atracurium in Rat Plasma ($n = 3$)

| | No treatment | | TOTP Treatment | | |
|---|---|---|---|---|---|
| | Duration of incubation (min) | | Duration of incubation (min) | | Pooled SEM |
| | 0 | 45 | 0 | 45 | |
| Residual twitch activity[a] (% of control) | 0 | 72.0 | 0 | 10.6 | 3.5 |
| Recovery rate (% recovered per min) | 43.6 | 24.9 | 44.5 | 43.9 | 6.1 |
| Body weight (g) | 244 | | 240 | | 13 |
| Arterial pH[b] | 7.32 | | 7.36 | | 0.04 |
| Arterial $P_{CO_2}$ (torr)[b] | 31.3 | | 31.6 | | 2.0 |
| Plasma pH[c] | 7.33 | | 7.34 | | 0.04 |

Atracurium was added to untreated or TOTP-treated plasma samples from rats and the samples were incubated for 45 minutes. Aliquots of plasma were collected at the start or at the end of incubation (duration of incubation 0 or 45 min, respectively) and injected intravenously to rats.

[a] Probabilities that the observed differences among the four groups were due to a chance observation were: for 0 vs 45 min of incubation $< 0.001$, for no treatment vs TOTP treatment $< 0.001$, and for interaction between these two factors $< 0.001$. Comparisons among the four groups for other parameters were not significant.

[b] Arterial blood sampled before termination of the experiments.

[c] Plasma pH was measured at the end of 45 min of incubation with atracurium.

ration of action. Recovery rate, however, was independent of the injected dose. No single parameter was, therefore, completely satisfactory for the definition of the dose–response relationship for atracurium over the whole range of doses tested. The data of this study, however, permitted us to select the optimal dose of atracurium (1.2 mg·kg$^{-1}$) and the optimal parameter to be used in the bioassay of atracurium present in aliquots of plasma. We decided to rely on measurements of the residual twitch activity as the principal parameter of muscle relaxation and to resort to other parameters solely to corroborate the findings.

The first experimental series was designed to measure the enzyme-catalyzed inactivation of atracurium in rat plasma in vitro (Table 2). When the aliquots of plasma were removed immediately after the addition of atracurium (0 min of incubation) and injected intravenously to rats, the responses were similar and independent of the level of enzyme activity (control or TOTP-treated plasma). In both groups the twitch response was completely abolished and recovered at approximately similar rates. At the end of the 45-min incubation period, the pH of the incubated solutions was 7.3, and there was no difference in pH between the control and TOTP-treated plasma samples. Marked differences were observed at this time, however, in pharmacologic responses to injections of the two samples. Injection of an aliquot of control plasma produced only a slight inhibition of the evoked contractions. In contrast, intravenous administration of an aliquot of the incubation mixture containing atracurium incubated in TOTP-treated plasma produced a marked inhibition of the evoked twitch. Statistical analysis showed that the changes in residual twitch activity ascribable to duration of incubation and to the treatment of plasma with TOTP were highly significant. For the purposes of this study, even more important was finding a highly significant interaction between the duration of incubation and the TOTP treatment. Significant interaction implies that the rate of inactivation was dependent on whether the incubation was performed in inhibited or uninhibited (control) plasma. Inactivation of atracurium proceeded at a slower rate in TOTP-treated than in control plasma. For reasons previously mentioned, utilization of the other parameters did not provide any additional information but merely confirmed the findings described earlier. These data were, therefore, omitted from Table 2. As was found in the dose–response study, recovery rate was independent of duration of incubation and TOTP treatment.

Inactivation of atracurium in human plasma was studied next (Table 3). Measurements of plasma pH before and immediately after the addition of atracurium and again at the end of incubation showed no changes attributable to TOTP treatment, addition of atracurium, or duration of incubation. Only the data obtained at the end of incubation are presented in Table 3. Intravenous injection of incubation aliquots collected immediately after the addition of atracurium reduced the residual twitch activity to about 1% of the preinjection value. The response produced by TOTP-treated plasma was comparable to that produced by untreated (control) plasma. Injection of plasma aliquots, collected at the end of 45 min of incubation, produced a significantly less marked muscle paralysis ($P < 0.001$) as indicated by the presence of sizable residual twitch activity in both groups. The responses, however, were comparable and independent of TOTP treatment. Interaction between the two factors was not present. Recovery rate (Table 3) and other measured parameters (data not presented) did not differ among the four groups.

Table 3. Incubation of Atracurium in Human Plasma ($n = 6$)

| | No treatment | | TOTP Treatment | | |
|---|---|---|---|---|---|
| | Duration of incubation (min) | | Duration of incubation (min) | | Pooled |
| | 0 | 45 | 0 | 45 | SEM |
| Residual twitch activity[a] (% of control) | 1.38 | 30.9 | 1.20 | 20.8 | 6.4 |
| Recovery rate (% recovered per min) | 41.0 | 42.4 | 38.3 | 35.9 | 3.7 |
| Body weight (g) | 312 | | 312 | | 11. |
| Arterial pH[b] | 7.40 | | 7.39 | | 0.03 |
| Arterial $P_{CO_2}$ (torr)[b] | 32.8 | | 34.7 | | 2.8 |
| Plasma pH[c] | 7.42 | | 7.44 | | 0.04 |

Atracurium was added to untreated or TOTP-treated human plasma samples and the samples were incubated for 45 min. Aliquots of plasma were collected at the start and at the end of incubation (duration of incubation 0 and 45 min, respectively) and injected intravenously to rats.

[a] Probabilities that the observed differences among the four groups were due to a chance observation were for 0 vs 45 min of incubation, $< 0.001$; for TOTP treatment vs no treatment, 0.439; and for interaction between these two factors, 0.455. Comparisons among the four groups for other parameters were not significant.

[b] Arterial blood was sampled before termination of the experiments.

[c] Plasma pH was measured at the end of 45 min of incubation with atracurium.

## Discussion

Preliminary experiments demonstrated that the design of our study was suitable to examine separately the postulated inactivation pathways of atracurium in human plasma in vitro. The initial step in the degradation of atracurium, be it either Hofmann elimination or ester hydrolysis, leads to pharmacologic inactivation of the drug as a muscle relaxant. We studied only this initial step and can draw no conclusions regarding the roles of either pathways in the subsequent degradation of the metabolites.

The higher residual twitch activity observed on injection of atracurium incubated for 45 min in control rat plasma (Table 2) as compared to that incubated in control human plasma (Table 3) may be ascribed to faster inactivation of atracurium in rat plasma. Because temperature and pH values of the incubation solutions were comparable, Hofmann elimination most likely proceeded at similar rates in plasma samples from both species. The faster inactivation in rat plasma, therefore, suggests that the inactivation of atracurium was facilitated by an additional process, presumably the enzyme-catalyzed hydrolysis. The suggestion is strengthened by the findings that TOTP treatment markedly slowed the inactivation of atracurium in plasma with high enzyme activity (rat) but had only minimal, if any, effect on atracurium inactivation in plasma with presumably lower activity (humans).

The claim of a dual degradation pathway of atracurium in humans is based only on scant evidence. In the experiments of Merrett et al. (3) atracurium was incubated in tris buffer or in human plasma. The concentration of atracurium remaining after incubation was assayed in mice using a loss of motor activity and a decrease in the frequency of breathing as the indicators of skeletal muscle relaxation. The authors reported that the mean half-life of atracurium in human plasma was approximately 45 min or about 1.8 times shorter than in tris buffer. They suggested that the faster rate of inactivation in plasma was due to the catalytic activity of nonspecific esterases; a role for plasma pseudocholinesterase was ruled out (3). To our knowledge there is no other evidence to support the proposal of enzyme-catalyzed inactivation in humans (or animals). We believe that the evidence presented by Merrett et al. is inadequate because their data are clearly open to a different interpretation: reaction of the products of Hofmann elimination with compounds present in plasma could have enhanced the rate of Hofmann elimination. Thus removal of the products of the elimination reaction occurring in plasma but not in a buffered solution may be considered as an alternative explanation. Our experiments were designed to circumvent this possibility.

Inactivation of atracurium in human plasma in vitro was slow and was only marginally susceptible to enzymatic catalysis (Table 3). Both findings indicate that the activity of carboxylesterase was low and that the enzyme-catalyzed hydrolysis probably did not constitute a major pathway in the inactivation of atracurium. A much larger number of donors would have to be studied to infer the role of the enzyme in the population at large.

Several other explanations of our findings with human plasma were considered. First, human plasma carboxylesterase might not have been inhibited by TOTP. Alternatively, atracurium might not be the optimal substrate for the human enzyme or it might be an inhibitor of the human but not the rat enzyme. Our present data and several reports from the literature permit us to reject these alternatives for the following reasons:

1) Our results show that the inactivation of atracurium proceeded markedly slower in human than

in rat plasma (Tables 2, 3). Determinations of in vitro half-life of atracurium incubated in plasma from different species (19) also showed a marked species variability. Because Hofmann elimination may be considered to have proceeded at similar rates in plasma from different species, the variability presumably reflected the contribution of the enzyme-catalyzed ester hydrolysis.

2) Atracurium was shown to be only a relatively weak inhibitor of human red cell acetylcholinesterase or plasma pseudocholinesterase (2,20). Although no direct information is available for carboxylesterase, a similarly weak inhibitory propensity may be presumed.
3) With methyl butyrate as a substrate, the activity of carboxylesterase was found to be about 10 times higher in rat than in human plasma (21).
4) Baraka et al. (22) reported that the duration of skeletal muscle relaxation produced by atracurium was not prolonged in a patient poisoned with parathion. Although they did not measure the activity of carboxylesterase in plasma, it is plausible to postulate that, along with other esterases, the enzyme carboxylesterase was inhibited by the organophosphorous insecticide. The findings of Baraka et al. can be explained if enzyme-catalyzed hydrolysis of atracurium represented a minor inactivation pathway in their patient.

We believe that all these findings taken together indicate that the role of enzyme-catalyzed ester hydrolysis of atracurium in human plasma is probably a minor one at best. By exclusion, Hofmann elimination appears to be the dominant inactivation pathway in humans. If so, the toxicologic aspects of the products of Hofmann elimination deserve detailed examination. The issue of possible toxic effects of laudanosine appears to have been satisfactorily resolved (9): when used in healthy patients in clinically recommended doses, atracurium is unlikely to produce toxic levels of laudanosine. The question of possible undesirable effects of acrylate (23) generated in vivo by Hofmann elimination of atracurium remains to be resolved.

Our special thanks to J. A. Levin, PhD, for providing laboratory space and equipment and to Mrs. J. Hakius for excellent help in preparation of the manuscript.

## References

1. Stenlake JB, Waigh RD, Dewar GH, Hughes R, Chapple DJ, Coker GG. Biodegradable neuromuscular blocking agents. Part 4. Atracurium besylate and related polyalkylene di-esters. Eur J Med Chem 1981;16:515–24.
2. Hughes R, Chapple DJ. The pharmacology of atracurium: a new competitive neuromuscular blocking agent. Br J Anaesth 1981;53:31–44.
3. Merrett RA, Thompson CW, Webb FW. In vitro degradation of atracurium in human plasma. Br J Anaesth 1983;55:61–6.
4. Neill EAM, Chapple DJ. Metabolic studies in the cat with atracurium: a neuromuscular blocking agent designed for non-enzymic inactivation at physiologic pH. Xenobiotica 1982;12:203–10.
5. Payne JP, Hughes R. Evaluation of atracurium in anaesthetized man. Br J Anaesth 1981;53:45–54.
6. Basta SJ, Ali HH, Savarese JJ, et al. Clinical pharmacology of atracurium besylate (BW 33A): a new non-depolarizing muscle relaxant. Anesth Analg 1982;61:723–9.
7. Hilgenberg JC. Comparison of the pharmacology of vecuronium and atracurium with that of other currently available muscle relaxants. Anesth Analg 1983;62:524–31.
8. Katz RL, Stirt J, Murray AL, Lee C. Neuromuscular effects of atracurium in man. Anesth Analg 1982;61:730–4.
9. Miller RD, Rupp SM, Fisher DM, Cronnelly R, Fahey MR, Sohn YJ. Clinical pharmacology of vecuronium and atracurium. Anesthesiology 1984;61:444–53.
10. Bevan DR. Neuromuscular blocking drugs. Can Anaesth Soc J 1983;30:S56–61.
11. Bowman WC. New neuromuscular blocking drugs in anaesthetic practice. Pharm Internat 1983;4:131–4.
12. Ward S, Neill EAM, Weatherley BC, Corall IM. Pharmacokinetics of atracurium besylate in healthy patients (after a single I.V. bolus dose). Br J Anaesth 1983;55:113–7.
13. Ward S, Neill EAM. Pharmacokinetics of atracurium in acute hepatic failure (with acute renal failure). Br J Anaesth 1983;55:1169–72.
14. Fahey MR, Rupp SM, Fisher DM, Miller RD, et al. The pharmacokinetics and pharmacodynamics of atracurium in patients with and without renal failure. Anesthesiology 1984;61:699–702.
15. Nigrovic V, Auen M, Wajskol A. Enzymatic hydrolysis of atracurium in vivo. Anesthesiology, in press.
16. Silver EH, Murphy SD. Potentiation of acrylate ester toxicity by prior treatment with the carboxylesterase inhibitor triorthotolyl phosphate (TOTP). Toxicol Appl Pharmacol 1981;57:208–19.
17. Nigrovic V, Pandya J, Auen M, Wajskol A. Enzyme-catalyzed hydrolysis (ECH) of atracurium (A) in human and rat plasma. Fed Proc 1985;44:503A.
18. Snedecor GW, Cochran WG. Statistical methods, 7th ed. Ames, Iowa: The Iowa State University Press, 1980:298–307.
19. Neill EAM, Chapple DJ, Thompson CW. Metabolism and kinetics of atracurium: An overview. Br J Anaesth 1983;55:23S–5S.
20. Foldes FF, Deery A. Protein binding of atracurium and other short-acting neuromuscular blocking agents and their interaction with human cholinesterase. Br J Anaesth 1983;55:31S–4S.
21. Tsujita T, Okuda H. Carboxylesterases in rat and human sera and their relationship to serum aryl acylamidases and cholinesterases. Eur J Biochem 1983;133:215–20.
22. Baraka A, Cava L, Jaoude CA. Atracurium v. suxamethonium in a case of organophosphorous poisoning. Br J Anaesth 1984;56:673.
23. Nigrovic V and Koechel D. Atracurium—additional information needed. Anesthesiology 1984;60:606–7.

ANESTH ANALG
1985;64:1053–9

# Effects of Fentanyl and Diazepam in Dogs Deprived of Autonomic Tone

Joan W. Flacke, MD, L. Jane Davis, MA, Werner E. Flacke, MD, Byron C. Bloor, PhD, and Aaron P. Van Etten, MS

FLACKE JW, DAVIS LJ, FLACKE WE, BLOOR BC, VAN ETTEN AP. Effects of fentanyl and diazepam in dogs deprived of autonomic tone. Anesth Analg 1985;64:1053–9.

*In contrast to reports of the untoward hemodynamic effects of fentanyl and diazepam in intact organisms, we found that neither a bolus of 100 μg/kg fentanyl nor the addition of intravenous doses of diazepam, up to and including 1 mg/kg (cumulative dose 2 mg/kg) caused cardiovascular depression in 13 anesthetized dogs after elimination of their sympathetic and parasympathetic tone. There were no significant changes in mean arterial blood pressure, cardiac output, heart rate, peak left ventricular dP/dt, cardiac filling pressures, or systemic vascular resistance. Rapid bolus injection of 3 mg/kg diazepam (cumulative dose 5 mg/kg) caused a significant ($P < 0.05$) but transient (time to 50% recovery less than 2 min) decrease in systemic vascular resistance, blood pressure, and dP/dt. When corrected for pressure changed (dP/dt divided by simultaneous left ventricular pressure), the decrease in dP/dt did not attain statistical significance, nor did changes in cardiac output or filling pressures, even after this large dose of diazepam. We conclude that previously reported decreases in hemodynamic function in subjects with intact autonomic function after fentanyl alone, or after the combination of fentanyl and diazepam, are indirect in nature, that is, are caused by a centrally mediated decrease in vasoregulatory (mainly sympathetic) outflow from the central nervous system.*

Key Words: HYPNOTICS, BENZODIAZEPINES—diazepam. ANALGESICS—fentanyl.

Clinical investigators have reported minimal effects of either diazepam (1) or fentanyl (2–4) upon the cardiovascular system when both drugs were used alone in doses sufficient to bring about unconsciousness. In order to utilize both the hypnosis and amnesia produced by the former and the profound analgesia caused by the latter, the combination of the two agents is frequently used in the anesthetic management of patients undergoing cardiac surgery. However, Stanley and Webster (2) have reported that the administration of 10 mg of diazepam, after the administration of 50 μg/kg fentanyl, to patients with mitral valve disease caused significant decreases in blood pressure, secondary to a fall in both systemic vascular resistance and cardiac output.

Similarly, Hoar et al. (5) found a decrease in cardiac output and a further decrease in blood pressure and in cardiac output when 0.3 mg/kg diazepam was given to patients with coronary artery disease who had previously received high doses of morphine. Elevated plasma catecholamine levels, which had risen (5) in response to morphine-induced vasodilatation (6,7), returned to control levels after the addition of the diazepam. More recently, Tomicheck et al. (8), in a study of the effects of different doses of diazepam (up to 0.5 mg/kg) given before administration of 50 μg/kg of fentanyl to patients with coronary artery disease, found significant (but not dose-dependent) decreases in blood pressure, systemic vascular resistance, and plasma catecholamines when the fentanyl was added. Yet, no cardiovascular changes occurred after fentanyl alone, i.e., in the patients who had not been pretreated with diazepam.

This hemodynamic stability after high doses of fentanyl alone has not been a universal finding. Our laboratory has recently demonstrated a non-dose-dependent, marked decrease in cardiovascular function, paralleled by decreased plasma catecholamine levels when fentanyl was administered to intact dogs lightly anesthetized with enflurane (9). Furthermore, patients also have been reported to sustain slight to

---

Received from the Department of Anesthesiology, University of California Los Angeles, School of Medicine, Center for the Health Sciences, Los Angeles, California. Accepted for publication June 4, 1985.

Address correspondence to Dr. J. W. Flacke, Department of Anesthesiology, University of California Los Angeles, School of Medicine, Center for Health Sciences, Los Angeles, CA 90024.

© 1985 by the International Anesthesia Research Society

moderate decreases in blood pressure when given fentanyl alone (3,10), and occasionally severe hypotension has occurred (11,12), even in the absence of vagally induced bradycardia. It has been postulated that these episodes are predominantly the result of narcotic-induced inhibition of central sympathetic outflow (9,11–13). Hence, an essential preexisting condition is a high degree of sympathetic tone.

Reves et al. (14) have reported direct negative inotropic effects in isolated rat heart muscle from fentanyl and diazepam, both singly and in combination. However, even with the high concentrations used in vitro, no synergistic or "supraadditive" effects of the two drugs could be demonstrated, leading the authors to speculate that the clinically reported synergistic effects might be occurring in the peripheral vascular bed rather than in the heart. It seemed to us that synergistic effects of the two drugs are just as likely to occur within the central nervous system; hence, we undertook the present study. The approach was to eliminate the central nervous system; the purpose was twofold. First, we wanted to ascertain further whether previously reported decreases in hemodynamic function after fentanyl alone were, in fact, indirect, in which case they should not occur in the absence of autonomic outflow from the central nervous system. Second, we wanted to determine whether or not the combination of fentanyl and diazepam may act synergistically to cause direct cardiovascular depression, or if the effects reported (2,8,15) are also due merely to further central inhibition. In order to separate direct from indirect effects mediated via the autonomic nervous system, we eliminated parasympathetic and sympathetic afferent and efferent mechanisms by vagotomy and subarachnoid sympathetic block, respectively.

## Methods

Anesthesia was induced with 20 mg/kg thiopental intravenously in 13 mongrel dogs (weight, 21.3 ± 1.0 kg). After intubation with a cuffed endotracheal tube, the dogs were ventilated with enflurane in oxygen via a Harvard piston pump to maintain normal blood gases and a blood enflurane concentration of 0.97 ± 0.04% as measured by gas chromatography (16). Body temperature, measured by an esophageal thermistor probe, was maintained at 38 ± 1°C with a warm water blanket. Cannulae were inserted into a femoral artery and vein for blood pressure measurements, arterial blood sampling, and administration of fluids and drugs. Lactated Ringer's solution with 5% dextrose was given at 100 ml/hr. A catheter tip transducer (Millar, model PC3470) was introduced into the left ventricle through the left carotid artery. A flow-directed balloon-tipped catheter was placed in the pulmonary artery via the right external jugular vein, and ECG electrodes were attached. To bring about parasympathetic block, the vagus nerves were isolated and cut in the neck. After surgical exposure of the posterior cervical region, a 20-gauge catheter was introduced through the atlanto–occipital membrane and threaded 15–20 cm into the thoracic subarachnoid space. Placement of the catheter was confirmed by aspiration of spinal fluid. After control observations were completed, one percent tetracaine, in 5 mg increments to a total dose of 20 mg, was injected into the subarachnoid space. Blood pressure decrease in response to the initial injection, lack of further decrease after the final 5 mg, and decreases in circulating catecholamines were taken as evidence of sympathetic block. Cardiac filling pressures were restored to prespinal levels with 6% high molecular weight dextran. Thirty min were allowed for equilibration, and fentanyl (100 μg/kg) was administered as a bolus.

Starting 10 min after the fentanyl injection, and at 10 min intervals thereafter, rapid bolus injections (< 1 min) of diazepam in increasing dosages from 0.1 to 3.0 mg/kg were given. Arterial samples for determination of plasma norepinephrine (NE) and epinephrine (EPI) were taken before and after spinal block and at intervals throughout the rest of the experiment. Hemodynamic measurements were taken before and 30 min after spinal block, and before and after fentanyl and each dose of diazepam.

Continuous hemodynamic measurements included arterial blood pressure (BP), pulmonary artery pressure (PAP), central venous pressure (CVP), left ventricular end diastolic pressure (LVEDP), ECG, and heart rate (HR). The instantaneous rate of rise of left ventricular pressure (*dP/dt*) and *dP/dt* over left ventricular pressure at that instant [(*dP/dt*)/*P*] were obtained electronically. All outputs were amplified and continuously recorded on an eight channel Hewlett–Packard polygraph (series 7758B), which in turn was interfaced with a MINC minicomputer (Digital Equipment Company, Model 11/23) for on line monitoring and later plotting (17). Thermodilution cardiac output (CO) was determined in triplicate with a Santa Barbara cardiac output computer.

Derived hemodynamic values were cardiac index (CI) = CO/BSA; systemic vascular resistance (SVR) = (MAP − CVP) × 80/CO; and systemic vascular resistance index (SVRI) = SVR × BSA. Plasma catecholamine samples were measured by a high performance liquid chromatography technique developed in this laboratory (18) that has recently been validated in an international study (19).

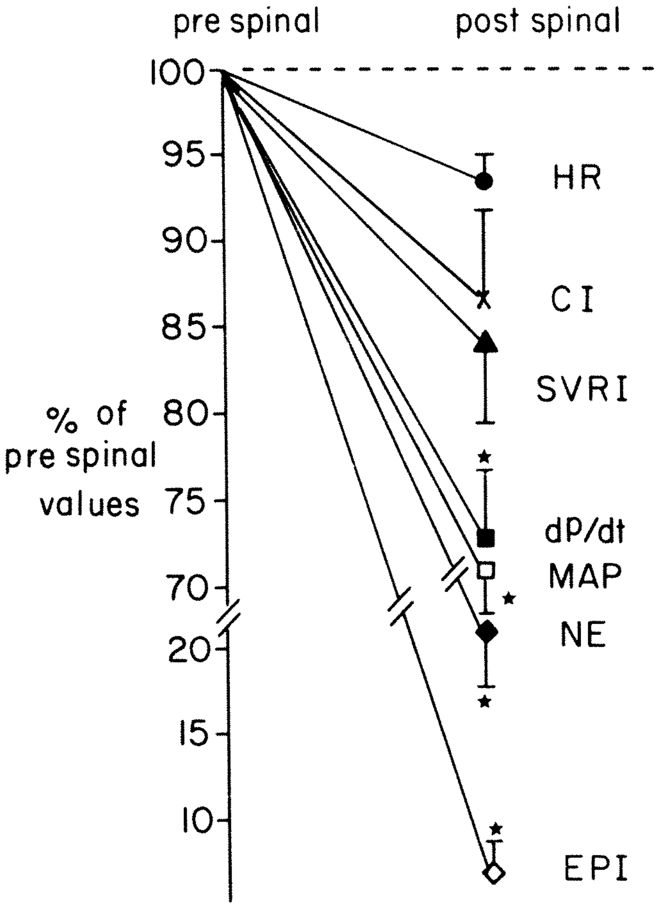


Figure 1. Percent changes (mean ± SEM) in hemodynamic data and plasma catecholamine levels brought about by vagotomy and thoracic subarachnoid sympathetic block in 13 dogs. Significant decreases ($P < 0.05$) were observed in mean arterial pressure (MAP), rate of rise of left ventricular pressure (*dP/dt*), and norepinephrine (NE), and epinephrine (EPI) values. Changes in heart rate (HR), cardiac index (CI), and systemic vascular resistance index (SVRI) were not significant.

All values are reported as mean ± SEM. Intragroup comparisons were made by analysis of variance for repeated measures, followed by Bonferroni's modified *t*-test when $P$ was $< 0.05$. Drugs used were commercial preparations of fentanyl citrate (Sublimaze, Janssen Pharmaceutica, NY), diazepam (Valium, Hoffman–LaRoche, NJ), tetracaine hydrochloride (Pontocaine, Breon Laboratories, NY), and thiopental sodium (Pentothal, Abbott Laboratories, IL).

## Results

Table 1. Pre-Fentanyl Hemodynamic Values and Plasma Catecholamine Levels[a]

| | | |
|---|---|---|
| Heart rate | 127 ± 5 | beats/min |
| MAP | 89 ± 6 | mm Hg |
| Cardiac index | 3.3 ± 0.2 | $L \cdot min^{-1} \cdot m^{-2}$ |
| Left ventricular end diastolic pressure | 7 ± 2 | mm Hg |
| Systemic vascular resistance index | 2135 ± 217 | $dyne \cdot sec \cdot cm^{-5} \cdot m^{2}$ |
| Norepinephrine | 18 ± 4 | pg/ml |
| Epinephrine | 33 ± 9 | pg/ml |

[a] After autonomic blockade but before fentanyl. Values are mean ± SEM; $n = 13$.

Percent decreases in cardiovascular parameters and plasma catecholamines brought about by subarachnoid block are depicted in Figure 1. All hemodynamic values, expressed as percent of prespinal levels, decreased. Circulating catecholamines dropped profoundly to 21 ± 3% (NE) and 7 ± 2% (EPI) of prespinal levels. Absolute values 30 min later are shown in Table 1 and these represent the control levels before either fentanyl or diazepam were given. Plasma catecholamines remained at these low levels throughout the experiment, NE being 18 ± 3 pg/ml and EPI 29 ± 9 pg/ml at the time when the protocol was completed. The mean time from the taking of post spinal, prefentanyl control values until the end of the experiment was 80 ± 5 min.

After autonomic block, fentanyl rapidly given intravenously at a dose of 100 μg/kg had no effect upon cardiovascular function, as illustrated in the tracing from a representative experiment (Fig. 2). (The slight increase in blood pressure seen in this figure was probably caused by rapid injection of the 45-ml volume of the fentanyl solution.) In the 13 experiments performed, this dose of fentanyl did not significantly change any of the hemodynamic parameters measured, as shown in Table 2.

Diazepam, given after the fentanyl in divided bolus doses of 0.1, 0.3, and 0.6 mg/kg, produced no changes in cardiovascular function. One mg/kg of diazepam caused small decreases in arterial blood pressure and systemic vascular resistance, without changes in cardiac output or left ventricular end-diastolic pressure (Fig. 3). However, in the group as a whole, these peak decreases after 1 mg/kg were not changed significantly from preinjection values, nor were they significantly different from the post-spinal, prefentanyl control values (Fig. 4). A dose of 3 mg/kg diazepam did cause a significant decrease in blood pressure, systemic vascular resistance, and left ventricular *dP/dt* (Figs. 3, 4). However, when *dP/dt* was corrected for the effect of the blood pressure fall (by dividing peak *dP/dt* by the instantaneously developed isovolumic left ventricular pressure), the decrease was no longer significant. Even with this highest dose of diazepam, the hemodynamic changes were transient (Fig. 5), and complete recovery took place except in one dog

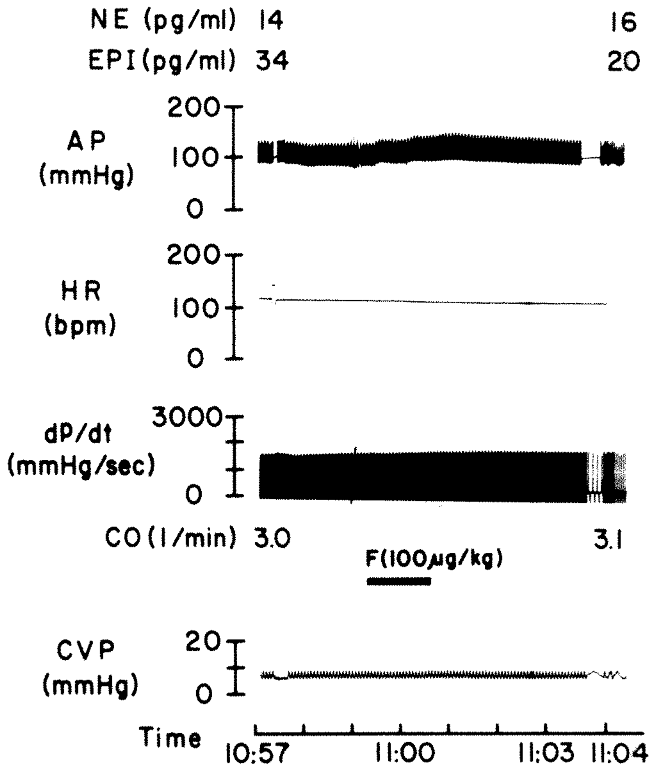


Figure 2. Tracing from a single experiment demonstrating the effects of 100 $\mu$g/kg fentanyl, given intravenously over 1.5 min to an autonomically blocked dog. Plasma catecholamines (NE and E), arterial blood pressure (AP), heart rate (HR), *dP/dt*, cardiac output (CO), and central venous pressure (CVP) are shown from the top down. No changes were seen except for a very slight and transient blood pressure rise. Compare with Figure 6.

which had persistent hypotension and eventually died after the largest dose of diazepam. (This dog had fever at the beginning of the experiment (42.5°C esophageal temperature) and was found to have bronchopneumonia at postmortem.) In all other animals cardiovascular values had returned to postspinal control values at the end of the experiment.

## Discussion

Although it is well established from laboratory and clinical reports that potent opioid analgesics sometimes cause a decrease in blood pressure, cardiac output, or both (2,9–13), and that the addition of diazepam to these compounds increases both the incidence and the severity of these hemodynamic events (3,5,8,15), it has been unclear whether the reported "synergistic" effects were direct or indirect, and what the mechanisms of these effects might be. This study demonstrates that in dogs in which central autonomic outflow had been eliminated, 100 $\mu$g/kg fentanyl caused no cardiovascular depressant effects (Fig. 2). In contrast, in our earlier series (9) in autonomically intact dogs anesthetized with enflurane–nitrous oxide, even one-tenth the dose of fentanyl caused a profound decrease of hemodynamic function (Fig. 6). In the present study, subsequent divided doses of diazepam up to and including 1 mg/kg also had no effect in these autonomically blocked dogs. Only with a bolus of 3 mg/kg diazepam, certainly an amount much larger than that used clinically, were depressant effects seen; that is, marked but transient hypotension secondary to vasodilatation brought about by decreased peripheral vascular tone. One might think that the decline in left ventricular *dP/dt* indicates that this large dose had some effect on cardiac function also, but this is spoken against by the fact that cardiac output did not decrease, LVEDP did not increase, and the change in *dP/dt* was not significant when an attempt was made to correct for the known effect upon this parameter (20) of the substantial decrease in arterial pressure. At any rate, the net physiologic effect of the decrease in systemic vascular resistance (SVR) was to allow cardiac function (output) to remain intact. From these studies we conclude that previously reported decreases (2,5,8–13,15) in cardiovascular function after fentanyl or clinically administered doses of diazepam in intact patients and animals must have been indirect in nature, that is, mediated by the autonomic nervous system. The role that reflex stimulation of the sympathoadrenal system plays in counteracting the direct depressant circulatory effects of anesthetic agents was pointed out for diethyl ether in 1953 by Brewster et al. (21) and has been aptly summarized by Price (22). However, the opposite side of the coin, i.e., the involvement of autonomic mechanisms, mainly central, in indirectly bringing about "depressant" effects of anesthetic drugs has not been as well characterized.

Table 2. Percent Changes From Fentanyl, 100 $\mu$g/kg[a]

| | |
|---|---|
| Heart rate | −4 ± 1% |
| MAP | +10 ± 2% |
| Cardiac index | −2 ± 3% |
| Left ventricular end diastolic pressure | 0 ± 0 torr |
| Systemic vascular resistance index | +1 ± 3% |
| *dP/dt*[b] | +6 ± 3% |

[a] Percent changes in values from before to after fentanyl. Values are mean ± SEM; $n$ = 13. No changes are statistically significant.

[b] Instantaneous rate of rise of left ventricular pressure.

In addition to their central vagotonic effects, opioids are well known to act upon central adrenergic mechanisms in an inhibitory manner (9,12,23). Generally,

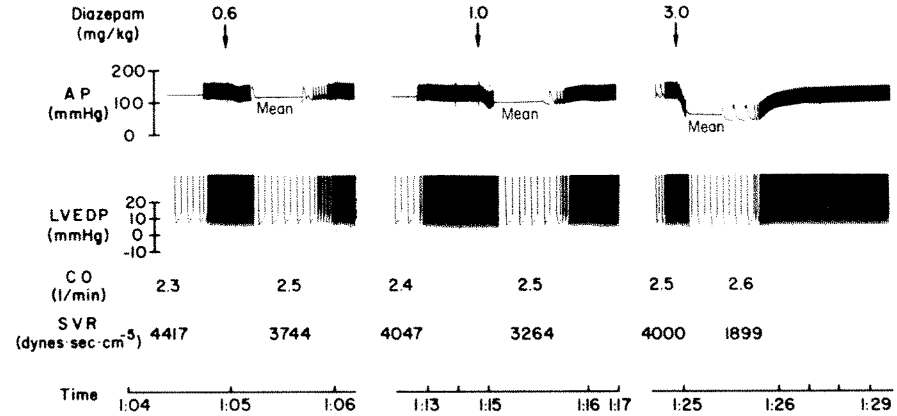
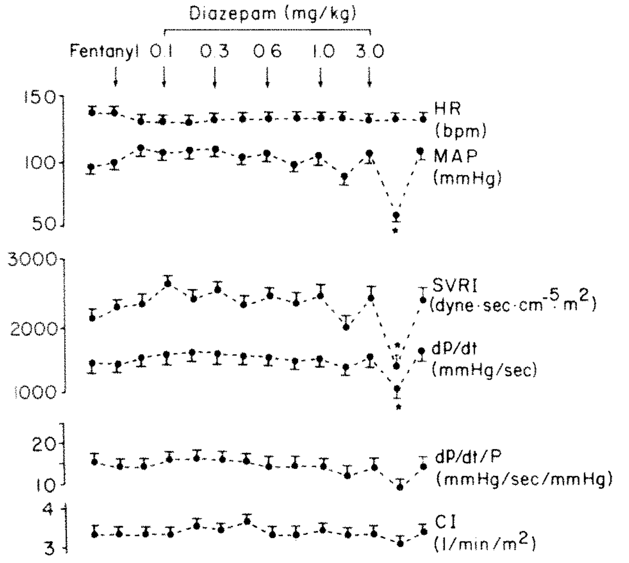


Figure 3. Representative tracing from a single experiment demonstrating the effects of bolus doses of 0.6, 1.0, and 3.0 mg/kg diazepam. From the top down are arterial pressure (mean pressure is displayed during peak changes), left ventricular diastolic pressure, cardiac output, and systemic vascular resistance.



* $p < 0.05$ when compared to control values (post spinal)

Figure 4. Mean ± SEM hemodynamic values (13 experiments). First points shown are the postspinal or prefentanyl control values. Other points are before and after (peak responses) fentanyl and before and after (peak responses) increasing doses of diazepam. From the top down are heart rate, mean arterial pressure, systemic vascular resistance index, peak *dP/dt*, peak *dP/dt* divided by instantaneous left ventricular pressure, and cardiac index. Starred values (*) are significantly different ($P < 0.05$) from postspinal control values; these significant decreases in mean arterial pressure, systemic vascular resistance index, and *dP/dt* occurred only after the largest dose (3 mg/kg) of diazepam.

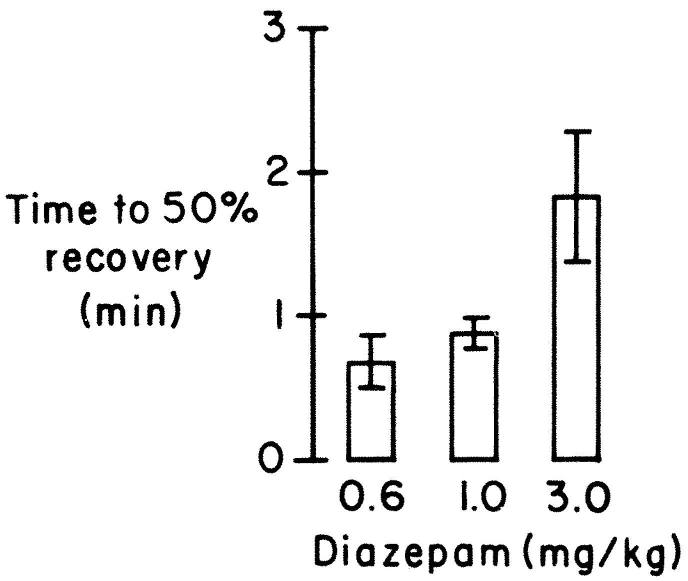


Figure 5. Time interval to 50% recovery of blood pressure decreases after 0.6, 1.0, and 3.0 mg/kg diazepam. For the first two doses, $n = 13$. For 3.0 mg/kg, $n = 12$, as one dog did not recover.

however, the resultant inhibition of central sympathetic outflow is counteracted by stimulatory effects from higher brain centers, as well as from ascending afferents, such as pain, temperature, and chemoreceptor fibers (12). For example, it is well known that both the respiratory depression and the hypotension seen in a narcotized but not profoundly depressed patient can be temporarily reversed to some extent by verbal and tactile stimulation. The fact that the addition of an anesthetic or hypnotic, such as nitrous oxide, thiopental, or diazepam, will then cause decreases in hemodynamic function, even if the opioid alone has not, is probably related to the ability of the latter drugs to eliminate these stimulatory mechanisms by deepening the central nervous system depression. That is, these drugs complete the putting to sleep process. A more remote possibility is that diazepam itself is more directly involved in central opiate mechanisms. In fact, some investigators (24,25) have reported that naloxone is able to reverse the

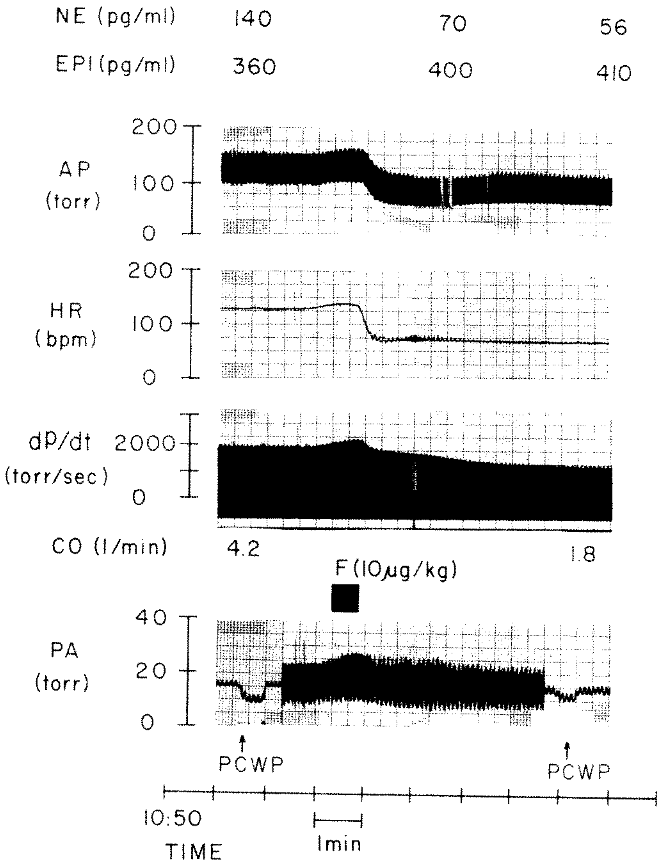


Figure 6. Tracing from a single experiment illustrating the response to an injection of 10 µg/kg fentanyl, given intravenously over 30 sec to an intact animal anesthetized with enflurane and nitrous oxide. Note the marked hemodynamic response to this small dose in this autonomically intact dog in contrast to the lack of changes after the 10-fold larger dose in the animal deprived of autonomic tone shown in Figure 2. (This figure is reproduced from (9) with permission.)

effects of diazepam upon the central nervous system; however, these findings have not been confirmed by others (26).

Regardless of the exact mechanism of the interaction, the distinction between efforts that occur because of inhibition of sympathetic outflow and those secondary to direct organ or system depression is an important one. Unlike direct drug effects, indirect ones would not be expected to exhibit typical dose–response relationships, and, indeed, such was the finding for diazepam in the study by Tomicheck et al. (8). On the contrary, both the incidence and the magnitude of autonomically mediated drug actions will depend upon the degree of preexisting autonomic activity; that is, these effects may be exaggerated in hyperadrenergic states brought about by fear, pain, hypovolemia, chronic hypertension, or congestive heart failure. In addition, centrally mediated decreases in hemodynamic function, unlike direct peripheral effects, are likely to be accompanied by decreased metabolic demands. Therefore, affected organs are less likely to have the ratio of oxygen supply to oxygen demand disturbed, resulting in a lesser incidence of tissue damage.

Finally, the normal cardiovascular system can function quite well in the absence of sympathetic tonic stimulation, as shown by the fact that complete ganglionic or adrenergic receptor block is compatible with normal hemodynamics, as long as postural changes are avoided (27). This demonstrates the most important difference between centrally and peripherally depressant drugs; the maximum effect of a centrally acting agent is the reduction of neurogenic outflow to zero, with the consequences described above. In contrast, the depression by peripherally acting drugs is dose-dependent and can extend to well below the level set by withdrawal of neurogenic tone.

## References

1. Knapp RB, Dubow HS. Diazepam as an induction agent for patients with cardiopulmonary disease. South Med J 1970;63:1451–3.
2. Stanley TH, Webster LR. Anesthetic requirements and cardiovascular effects of fentanyl–oxygen and fentanyl–diazepam–oxygen anesthesia in man. Anesth Analg 1978;57:411–6.
3. Lunn JK, Stanley TH, Eisele J, Webster L, Woodward A. High dose fentanyl anesthesia for coronary artery surgery: plasma fentanyl concentrations and influence of nitrous oxide on cardiovascular concentrations and influence of nitrous oxide on cardiovascular responses. Anesth Analg 1979;58:390–5.
4. Waller JL, Hug CC, Nagle DM, Craver JM. Hemodynamic changes during fentanyl–oxygen anesthesia for aortocoronary bypass operation. Anesthesiology 1981;55:212–7.
5. Hoar PF, Nelson NT, Mangano DT, Bainton CR, Hickey RF. Adrenergic response to morphine-diazepam anesthesia for myocardial revascularization. Anesth Analg 1981;60:406–11.
6. Philbin DM, Moss J, Akins CW, Rosow CE, Kono K, Schneider RC, VerLee TR, Savarese JJ. The use of H1 and H2 histamine agonists with morphine anesthesia: a double-blind study. Anesthesiology 1981;55:292–6.
7. Rosow CE, Moss J, Philbin DM, Savarese JJ. Histamine release during morphine and fentanyl anesthesia. Anesthesiology 1982;56:93–6.
8. Tomicheck RC, Rosow CE, Philbin DM, Moss J, Teplick RS, Schneider RC. Diazepam–fentanyl interaction–hemodynamic and hormonal effects in coronary artery surgery. Anesth Analg 1983;62:881–4.
9. Flacke JW, Flacke WE, Bloor BC, Olewine S. Effects of fentanyl, naloxone and clonidine on hemodynamics and catecholamine levels in dogs. Anesth Analg 1983;62:305–13.
10. Stanley TH, Philbin DM, Coggins CH. Fentanyl–oxygen anaesthesia for coronary artery surgery: cardiovascular and antidiuretic hormone responses. Can Anaesth Soc J 1979;26:168–72.
11. Lowenstein E, Philbin DM. Narcotic "anesthesia" in the eighties. Anesthesiology 1981;55:195–7.
12. Flacke WE, Flacke JW. Cardiovascular physiology and circulatory control. Seminars in Anesthesia. Orlando, FL: Grune & Stratton, Inc., 1982;1:185–95.

13. Howie MB. The experts opine. Survey of Anesthesiology 1982;26:128–9.
14. Reves JG, Kissin I, Fournier SE, Smith LR. Additive negative inotropic effect of a combination of diazepam and fentanyl. Anesth Analg 1984;63:97–100.
15. Roach GW, Moldenhauer CC, Hug CC, Schultz JD, Curling PE. Hemodynamic responses to fentanyl or diazepam–fentanyl anesthesia in patients in chronic nifedipine therapy. Anesthesiology 61:A374, 1984.
16. Fink BR, Morikawa K. A simplified method for the measurement of volatile anesthetics in blood by gas chromotography. Anesthesiology 1970;32:451–5.
17. Bloor BC, Flacke WE, Olewine S, Flacke JW. A "basic" cardiovascular data acquisition and processing system for the MINC 11/23. Computing in Anesthesia Internat Sympo, Feb 1982.
18. Watson E. Liquid chromatography with electrochemical detection for plasma norepinephrine and epinephrine. Life Sci 1981;28:493–7.
19. Hjemdahl P. Interlaboratory comparison of plasma catecholamine determinations using several different assays. Acta Physiol Scand 1984;suppl.527:43–54.
20. Wallace AG, Skinner S, Mitchell JH. Hemodynamic determinants of the maximal rate of rise of left ventricular pressure. Am J Physiol 1963;205:30–6.
21. Brewster WR, Isaacs JP, Waino-Anderson T. Depressant effect of ether on myocardium of the dog and its modification by reflex release of epinephrine and nor-epinephrine. Am J Physiol 1953;175:399–414.
22. Price HL. Circulatory actions of general anesthetic agents and the homeostatic roles of epinephrine and norepinephrine in man. Clin Pharmacol Ther 1961;2:163–76.
23. Laubie M, Schmitt H, Canellas J, Roguebert J, Demichel P. Centrally mediated bradycardia and hypotension induced by narcotic analgesics: dextromoramide and fentanyl. Eur J Pharmacol 1974;28:66–75.
24. Bell EF. The use of naloxone in the treatment of diazepam poisoning. J Pediatr 1975;87:803–4.
25. Duka T, Millan MJ, Ulsamer B, Doenicke A. Naloxone attenuates the anxiolytic action of diazepam in man. Life Sci 1982;31:1833–6.
26. Kraynack B, Gintautas J, Hughston T, DeShan D. Failure of naloxone to antagonize diazepam induced narcosis in rats. Proc West Pharmacol Soc 1981;24:189–90.
27. Paton WDM, Zaimis EJ. The methonium compounds. Pharmacol Rev 1952;4:219–53.

1060 ANESTH ANALG
1985;64:1060–4

# Electrophysiologic Effects of Enflurane and Halothane on Isolated Rabbit Hearts in the Presence and Absence of Metabolic Acidosis

Suzuko Ozaki, MD, Yasuyuki Gotoh, MD, Haruaki Nakaya, MD, Mitsue Azuma, MPhar, and Morio Kanno, MD

OZAKI S, GOTOH Y, NAKAYA H, AZUMA M, KANNO M. Electrophysiologic effects of enflurane and halothane on isolated rabbit hearts in the presence and absence of metabolic acidosis. Anesth Analg 1985;64:1060–4.

*Electrophysiologic effects of halothane and enflurane in the presence of a normal pH and during metabolic acidosis were examined in isolated rabbit hearts perfused at a constant rate. During exposure to a normal pH, both halothane and enflurane produced concentration-dependent suppression of sinus node automaticity and atrioventricular conduction. Intraatrial and intraventricular conduction times during constant pacing were slightly but significantly prolonged by these anesthetics at 2 MAC. The magnitudes of these electrophysiologic changes were similar with halothane and enflurane when compared at the same MAC. These electrophysiologic effects became more marked during metabolic acidosis (pH 6.9). These results suggest that enflurane and halothane have direct depressant actions on the cardiac conduction system and that these electrophysiologic effects may be augmented by metabolic acidosis.*

Key Words: ANESTHETICS, VOLATILE—halothane, enflurane. HEART, conduction systems.

Many clinical reports indicate that several volatile anesthetics produce cardiac arrhythmias such as sinus bradycardia, atrioventricular conduction block, and arrhythmias resulting from disturbances in automaticity, conduction, or both (1–6). There are also many studies in which electrophysiologic effects of volatile anesthetics have been evaluated in intact animals (7–10). However, in these in vivo studies the direct action of the anesthetics may have been modified by alterations of central autonomic tone because these agents also affect vagal and sympathetic tone (11). Hemodynamic changes, including a decrease in coronary perfusion pressure after the induction of volatile agents, might also influence electrophysiologic events. Therefore, in the present study the direct effects of halothane and enflurane, two inhalation anesthetics frequently used in clinical settings, on the automaticity and the conduction system were examined and compared in isolated rabbit hearts perfused at a constant flow rate. Another purpose of the present study was to determine whether the electrophysiologic actions of these agents are modified by acidosis, because acidosis reportedly influences the electrophysiologic properties of the cardiac conduction system (12–14).

## Methods

Thirty-two rabbits of either sex weighing 1.7–2.5 kg were given heparin intravenously (300 units/kg) before being sacrificed by a blow on the head. Their hearts were removed immediately and immersed in a modified Tyrode's solution with the following composition (mM): NaCl, 128; KCl, 5; $MgCl_2$, 0.5; $NaH_2PO_4$, 0.4; $NaHCO_3$, 22; $CaCl_2$, 1.8; and glucose, 5. After extraneous fat and connective tissue were removed, the heart was perfused, according to a noncirculating Langendorff technique, with the salt solution equilibrated with 95% $O_2$ + 5% $CO_2$ (pH 7.441 ± 0.013) at 37 ± 1°C. The acidic solution had the same composition as the normal solution with the exception of $NaHCO_3$, 8 mM, and NaCl, 142 mM. This solution, also equilibrated with 95% $O_2$ ± 5% $CO_2$, had a pH of 6.89 ± 0.01. The perfusate was pumped by a peristaltic pump (Tokyo Rika MP-1011) at a constant rate of 20 ml/min.

Halothane and enflurane were introduced into a reservoir of Tyrode's solution through calibrated vaporizers (Flotec Mark 3, Enflutec Mark 3), which were set for 1 or 2 MAC using the oxygen–carbon dioxide mixture as a carrier gas. The actual concentrations of

---

Received from the Departments of Anesthesiology and Pharmacology, Hokkaido University School of Medicine, Sapporo, Japan. Accepted for publication June 4, 1985.

Address correspondence to Dr. Gotoh, Department of Anesthesiology, Hokkaido University School of Medicine, Sapporo 060, Japan.

© 1985 by the International Anesthesia Research Society

halothane and enflurane in the perfusate were determined by gas chromatography (Shimadsu Gas Chromatograph GC-4A PTF). The perfusate was sampled from the perfusion line at the level just above the inlet to the heart. No measurable amount of anesthetic was detected in the perfusate during the control periods. During the exposure to anesthetics, concentrations in the perfusate were as follows: halothane, 5.0 ± 0.7 mg/dl at the 1 MAC setting, 9.3 ± 1.1 mg/dl at 2 MAC; enflurane, 11.3 ± 2.4 mg/dl at the 1 MAC setting, 20.3 ± 4.6 mg/dl at 2 MAC.

Two bipolar plunge wire electrodes were inserted into the left atrium and the apex. They were used as stimulus electrodes for the atrial and ventricular pacing at a rate of 180 beats/min. Pacing stimuli were rectangular pulses of 2 msec duration and slightly above the threshold, which were delivered from an electronic stimulator (Nihon Kohden SEN-3101) through an isolation unit (Nihon Kohden SS-101J). Three bipolar electrodes were inserted into the right atrium, the ventricular septum, and the left ventricle posterior wall in order to record intramyocardial electric activities. Bipolar electrograms obtained from these electrodes were amplified by a DC amplifier (San-ei Sokki 1236) at a time constant of 0.001 sec, and displayed on a memory oscilloscope equipped with a microcomputer (San-ei Sokki 2G56). These recordings were stored on a four-channel magnetic tape recorder (Sony DFR-3515) at a tape speed of 19 cm/sec and were replayed at a speed of 1.9 cm/sec for detailed analysis and for transfer to a photographic recorder (San-ei Sokki Visigraph 5L). This method allowed us to measure the following time intervals with an accuracy in a range of ± 0.2 msec when the deflection of the bipolar electrogram remained sharp. The interval between the two successive bipolar electrograms recorded from the right atrium during spontaneous firing was designated as sinus cycle length (SCL). Under the constant atrial pacing, the time intervals from the stimulus artifact to the peak of the bipolar electrograms, which were recorded from the right atrium and the ventricular septum, were designated as intraatrial conduction time (IACT) and atrioventricular conduction time (AVCT), respectively. The time interval between the stimulus artifact and the ventricular electrogram, i.e., intraventricular conduction time (IVCT), also was measured during the constant ventricular stimulation.

Thirty-two hearts were divided into four groups: hearts perfused with the normal solution containing halothane ($n = 8$) or enflurane ($n = 8$), and hearts perfused with the acidic solution containing halothane ($n = 8$) or enflurane ($n = 8$). After an equilibration period of 30 min, control measurements were made, and the hearts were perfused for 30 min with the medium containing low (1 MAC) or high (2 MAC) concentrations of anesthetics. In the studies of acidosis, the hearts were perfused with the acidic solution for 30 min prior to the introduction of the anesthetics. As separately confirmed from observations of four hearts, a 2-hr perfusion without any anesthetics produced no significant changes in any of the parameters.

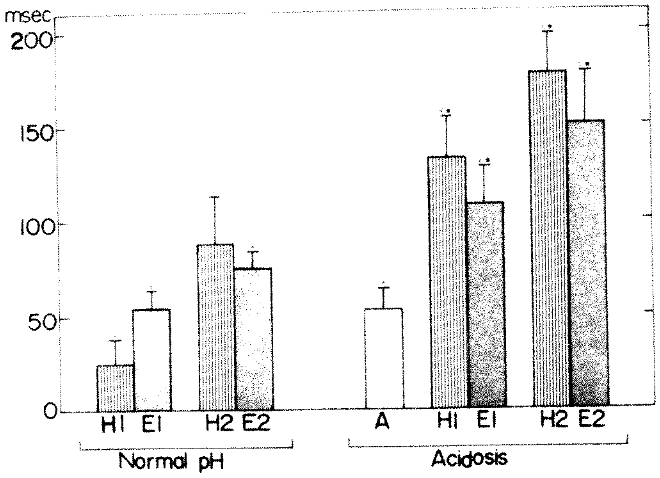


Figure 1. Effects of halothane and enflurane on sinus cycle length (SCL) in the absence or presence of acidosis. Changes in SCL are on the ordinates. H1, H2, E1, and E2 represent 1 MAC, 2 MAC of halothane, 1 MAC and 2 MAC of enflurane, respectively. SCL prolongation after acidosis alone is represented by A. Symbols: *, significant difference ($P < 0.05$) from control (baseline) values; ★, significant difference from the values after acidosis.

All data are presented as mean values ± standard errors. Changes in time intervals from baseline values after acidosis or the exposure to anesthetic agents were analyzed by the paired *t*-test. Statistical significance was assumed present when probability estimates decreased below the 5% level.

## Results

The baseline values of estimated time intervals from 32 hearts were as follows: SCL, 358.1 ± 16.8 msec; IACT, 24.9 ± 1.3 msec; AVCT, 87.0 ± 2.9 msec; and IVCT, 20.9 ± 2.2 msec. There were no significant differences in any of these time intervals among the four subgroups.

Halothane (H) and enflurane (E), both produced concentration-dependent prolongation of SCL, and the prolongation was augmented in the presence of metabolic acidosis (Fig. 1). Enflurane at 1 MAC (E1) and 2 MAC (E2) significantly increased SCL by 13.4 ± 2.5% and 19.4 ± 2.3%, respectively. The increases were similar to those produced by halothane at 1 MAC (H1) and 2 MAC (H2). Acidosis (A) was

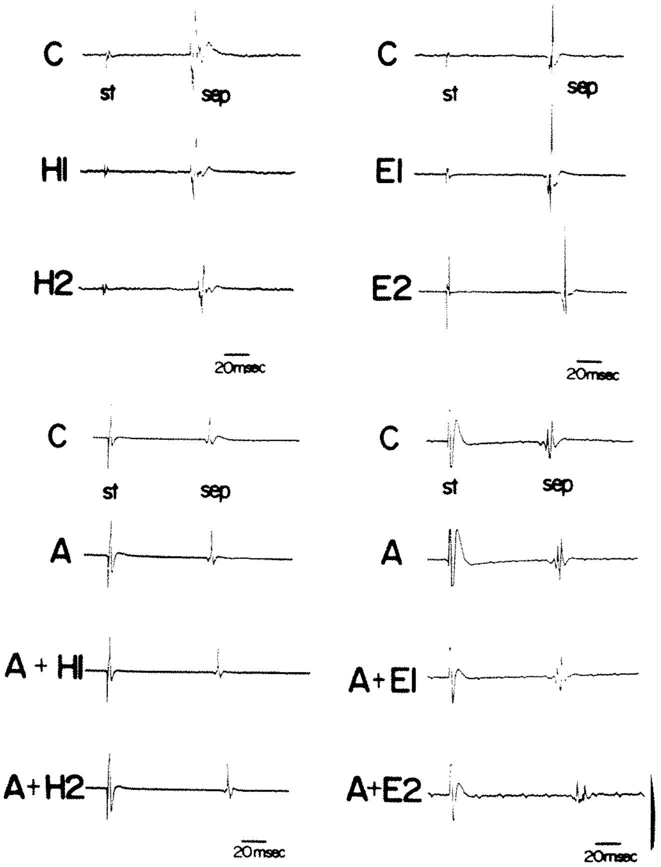


Figure 2. Changes of atrioventricular conduction time after halothane (*left panels*) and enflurane (*right panels*) in the absence (*upper panels*) or presence of acidosis (*lower panels*). C and A indicate bipolar electrograms recorded during the control period and after metabolic acidosis, respectively. H1, H2, E1, and E2 are the same as in Figure 1. Note that atrioventricular conduction times, the time intervals between stimulus artifact of the left atrial pacing impulse (st) and bipolar electrogram of ventricular septum (sep), were dose-dependently prolonged by these anesthetics, and the prolongation was augmented in the presence of acidosis.

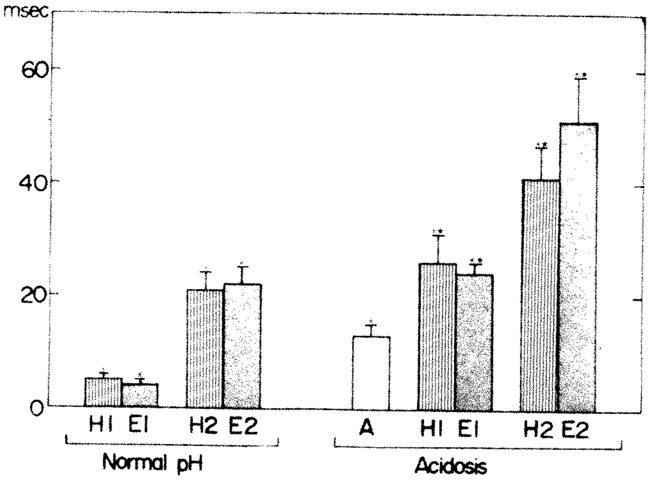


Figure 3. Effects of halothane and enflurane on atrioventricular conduction time (AVCT) in the absence or presence of acidosis. Changes in AVCT are on the ordinates in msec. Abbreviations are the same as in Figure 1. Symbols: * and ★ indicate statistical significance ($P < 0.05$) from the control values and the values after acidosis, respectively.

with a significant increase in SCL (13.0 ± 3.2%) and potentiated the prolongation of SCL induced by the volatile anesthetics.

Enflurane and halothane also produced concentration-dependent prolongation of AVCT, and these effects were augmented in the presence of acidosis. Figure 2 shows representative examples of AVCT prolongation after E or H when pH was normal and low. Halothane and enflurane prolonged AVCT to the same extent at equal MAC levels (Fig. 3). Acidosis alone significantly increased AVCT from 88.7 ± 3.0 msec to 101.4 ± 2.4 msec in 16 hearts ($P < 0.01$). Increases in AVCT during the exposure to H or E were enhanced by acidosis.

Effects of these anesthetics on IACT and IVCT are summarized in Tables 1 and 2. Although neither IACT nor IVCT was significantly affected by 1 MAC of these anesthetics in the presence of normal pH, these conduction times were slightly but significantly increased by 2 MAC of both anesthetics. Acidosis also slightly prolonged IACT and IVCT by 2.2 ± 0.5 msec and 3.9 ± 0.9 msec, respectively. Under acidic conditions, either IACT or IVCT was significantly increased from the preanesthetic values by 1 MAC of these anesthetics. Thus changes after anesthetics in IACT and IVCT, as well as AVCT and SCL, were augmented in the presence of acidosis.

## Discussion

The principal findings of the present study can be summarized as follows. Automaticity of the sinoatrial node and conduction of the atrioventricular node were depressed in a concentration-dependent manner by enflurane and halothane in isolated Langendorff-perfused rabbit hearts. These anesthetics slightly but significantly impaired intraatrial and intraventricular conduction at higher concentrations (2 MAC). The magnitude of electrophysiologic changes associated with enflurane were similar to those observed with halothane when compared at equal MAC levels. Metabolic acidosis (pH 6.9) augmented the electrophysiologic effects of the volatile anesthetics.

Studies of the direct effects of volatile anesthetics on the automaticity of the sinoatrial node have produced variable results. Krishna and Paradise (15), for example, found that enflurane elicited a concentration-dependent increase in heart rate, whereas halothane decreased heart rate at lower concentrations

Table 1. Effects of Halothane and Enflurane on Intraatrial Conduction Time (msec) in the Absence or Presence of Metabolic Acidosis

| | | Control | Acidosis | 1 MAC | 2 MAC |
|---|---|---|---|---|---|
| H | (*n* = 8) | 23.4 ± 2.0 | — | 23.8 ± 2.0 | 25.7 ± 2.3[a] |
| A + H | (*n* = 8) | 25.6 ± 1.1 | 27.7 ± 0.9[a] | 29.6 ± 1.1[a,b] | 32.3 ± 1.7[a,b] |
| E | (*n* = 8) | 26.2 ± 1.4 | — | 27.8 ± 1.6 | 32.1 ± 2.3[a] |
| A + E | (*n* = 8) | 24.4 ± 0.7 | 26.8 ± 1.1[a] | 28.4 ± 0.9[a,b] | 37.3 ± 4.0[a,b] |

Abbreviations: H, halothane; E, enflurane; A, acidosis.
Values are expressed as mean ± SEM.
[a] $P < 0.05$ from the control values.
[b] $P < 0.05$ from the values after acidosis by paired *t*-test.

Table 2. Effects of Halothane and Enflurane on the Intraventricular Conduction Time (msec) in the Absence or Presence of Metabolic Acidosis

| | | Control | Acidosis | 1 MAC | 2 MAC |
|---|---|---|---|---|---|
| H | (*n* = 8) | 19.1 ± 2.4 | — | 19.6 ± 2.0 | 23.1 ± 2.2[a] |
| A + H | (*n* = 8) | 24.6 ± 2.4 | 27.0 ± 2.3[a] | 30.1 ± 1.5[a,b] | 33.4 ± 1.3[a,b] |
| E | (*n* = 8) | 18.7 ± 2.5 | — | 21.0 ± 2.5 | 25.2 ± 2.4[a] |
| A + E | (*n* = 8) | 21.3 ± 1.7 | 26.6 ± 2.3[a] | 28.3 ± 2.3[a,b] | 33.8 ± 2.2[a,b] |

Abbreviations: H, halothane; E, enflurane; A, acidosis.
Values are expressed as mean ± SEM.
[a] $P < 0.05$ from the control values.
[b] $P < 0.05$ from the values after acidosis by paired *t*-test.

and increased it at higher concentrations in isolated rat atrial preparations. They also demonstrated that these effects were not blocked by propranolol or atropine. In contrast, earlier studies (16–18) and a recent report (19) showed that halothane and enflurane suppressed automaticity of the sinoatrial node. Our results are in line with the latter findings. Both anesthetics suppressed sinoatrial node function to the same extent at equal MAC levels, but, because our studies were done in vitro, we know the suppression does not involve influencing the tone of the autonomic nervous system. Like the in vivo studies by Atlee et al. (8–10), our study shows that halothane and enflurane also produced concentration-dependent prolongation of atrioventricular conduction in isolated rabbits hearts. Because it is well known that the action potentials of these cardiac tissues depend largely on $Ca^{2+}$ influx via slow channels, the observed inhibitory effects on these anesthetics may stem from the blocking action on the slow channels, as suggested by Lynch et al. (20). However, Bosnjak and Kampine (19) have suggested that the negative chronotropic effect of halothane and enflurane cannot be explained solely on the basis of the inhibitory action on the slow ionic current because it was not reversed by increasing extracellular calcium concentrations.

Halothane reportedly increases His–Purkinje and ventricular conduction times in dogs (10). However, Atlee et al. reported that 2 MAC of enflurane failed to affect the His–Purkinje and ventricular conduction time, which might mean less possibility of the occurrence of arrhythmias with enflurane than with halothane (9,21). In the present study, 2 MAC of these anesthetics slightly but significantly increased the intraatrial and intraventricular conduction times to the same extent. Some controversy exists as to whether halothane depresses the maximum upstroke velocity of phase 0 ($\dot{V}_{max}$), one of the major determinants of conduction velocity, in fast-response fibers such as Purkinje fibers and ventricular muscles. Hauswirth (22) demonstrated that 2% halothane depressed $\dot{V}_{max}$ in sheep Purkinje fibers. However, Lynch et al. (20) and Purnet et al. (23) reported that neither enflurane nor halothane depressed $\dot{V}_{max}$ in canine Purkinje fibers and guinea pig ventricular muscles. Whether or not these anesthetics depress $\dot{V}_{max}$ and conduction velocity in fast response fibers must be defined by further experimentation.

Acidosis has been reported to depress sinus node automaticity (12) and to decrease conduction velocity and $\dot{V}_{max}$ in Purkinje and ventricular muscle fibers (13,14). These depressant effects may be ascribed to the inhibitory action of hydrogen ions on inward $Na^+$ and $Ca^{2+}$ currents (24). In the present study, metabolic acidosis (pH 6.9) increased the depressant action of volatile anesthetics on the cardiac conduction system. Therefore, the inhibitory action of these anesthetics on slow and fast channels may be augmented under acidic conditions, although the underlying mechanism remains unclarified.

The results presented here indicate that enflurane and halothane have a direct depressant action on the cardiac conduction system, and it can be augmented in the acidic condition. These actions may be potentially deleterious to the heart with impaired automaticity or conduction, especially when it is under acidosis.

## References

1. Logic JR, Morrow DH. The effects of halothane on ventricular automaticity. Anesthesiology 1972;36:107–11.
2. Eickard B, Sorensen B. Arrhythmia during halothane anesthesia I: the influence of atropine during induction with intubation. Acta Anesthesiol Scand 1976;20:296–306.
3. Pratila MG, Pratilas V, Smith H. Dysrhythmias and enflurane anesthesia. Mt Sinai J Med 1979;46:500–4.
4. Wright CJ. Dysrhythmias during oral surgery: a comparison between halothane and enflurane anaesthesia. Anaesthesia 1980;35:775–8.
5. Lindgren L. E.C.G. changes during halothane and enflurane anaesthesia for E.N.T. surgery in children. Br J Anaesth 1981;53:653–62.
6. Willatts DG, Harrison AR, Groom JF, Crowther A. Cardiac arrhythmias during outpatient dental anaesthesia: comparison of halothane with enflurane. Br J Anaesth 1983;55:399–403.
7. Turner LA, Zuperku EJ, Purtock RV, Kampine JP. In vivo changes in canine ventricular cardiac conduction during halothane anesthesia. Anesth Analg 1980;59:327–34.
8. Atlee JL III, Rusy BF. Halothane depression of A-V conduction studied by electrograms of the bundle of His in dogs. Anesthesiology 1972;36:112–8.
9. Atlee JL III, Rusy BF. Atrioventricular conduction times and atrioventricular nodal conductivity during enflurane anesthesia in dogs. Anesthesiology 1977;47:498–503.
10. Atlee JL III, Alexander SC. Halothane effects on conductivity of the AV node and His–Purkinje system in the dog. Anesth Analg 1977;56:378–85.
11. Yamamura T, Kimura T, Furukawa K. Effects of halothane, thiamyl, and ketamine on central sympathetic and vagal tone. Anesth Analg 1983;62:129–34.
12. Satoh H, Hashimoto K. Effect of pH on the sino–atrial node cells and atrial muscle of dog. Arch Int Pharmacodyn 1983;261:67–78.
13. Kagiyama Y, Hill JL, Gettes LS. Interaction of acidosis and increased extracellular potassium on action potential characteristics and conduction in guinea pig ventricular muscle. Circ Res 1982;51:614–23.
14. Spitzer KW, Hogan PM. The effects of acidosis and bicarbonate on action potential repolarization in canine cardiac Purkinje fibers. J Gen Physiol 1979;73:199–218.
15. Krishna G, Paradise RR. Mechanisms of chronotropic effects of volatile inhalation anesthetics. Anesth Analg 1977;56:173–81.
16. Hauswirth O, Schaer H. Effects of halothane on the sino–atrial node. J Pharmacol Exp Ther 1967;158:36–9.
17. Reinolds AK, Chiz JF, Pasquet AF. Halothane and methoxyflurane: a comparison of their effects on cardiac pacemaker fibers. Anesthesiology 1970;33:602–10.
18. Porius AJ, van Zwieten PA. Quantitative evaluation of the cardiodepressive action of halothane and some related drugs in isolated heart muscle: comparison with in vivo circumstances. Arch Int Pharmacodyn 1973;205:134–43.
19. Bosnjak ZJ, Kampine JP. Effects of halothane, enflurane, and isoflurane on the sinus node. Anesthesiology 1983; 58:314–21.
20. Lynch C III, Vogel S, Sperelakis N. Halothane depression of myocardial slow action potentials. Anesthesiology 1981;55:360–8.
21. Atlee JL, Rusy BF, Kreul JF, Eby T. Supraventricular excitability in dogs during anesthesia with halothane and enflurane. Anesthesiology 1978;49:407–13.
22. Hauswirth O. Effects of halothane on single atrial, ventricular, and Purkinje fibers. Circ Res 1969;24:745–50.
23. Pruett JK, Mote PS, Grover TE, Augeri JM. Enflurane and halothane effects on cardiac Purkinje fibers. Anesthesiology 1981;55:A65.
24. Chesnais JM, Coraboeuf E, Sauviat MP, Vassas JM. Sensitivity to H, Li and Mg ions of slow inward sodium current in frog atrial fibers. J Mol Cell Cardiol 1975;7:627–42.

# Morphine Kinetics and Kidney Transplantation:

## Morphine Removal is Influenced by Renal Ischemia

John Sear, PhD, FFARCS, Andrew Moore, DPhil, FRSC, Adrian Hunniset, BSc,
Dene Baldwin, MLSO, Michael Allen, BSc, Christopher Hand, BSc, Henry McQuay, FFARCS,
and Peter Morris, PhD, FRACS, FRCS

SEAR J, MOORE A, HUNNISET A, BALDWIN D, ALLEN M, HAND C, McQUAY H, MORRIS P. Morphine kinetics and kidney transplantation: morphine removal is influenced by renal ischemia. Anesth Analg 1985;64:1065–70.

*Morphine plasma concentrations were determined in six patients receiving kidney transplants from living-related donors, and nine patients receiving kidney transplants from cadavers. The total cold ischemic time was about 2 hr for kidneys from living-related donors and 14 hr for those from cadavers. After an intravenous bolus dose of morphine, plasma morphine concentrations decreased to a plateau that lasted for several hours; morphine elimination resumed when the transplanted kidney began to clear creatinine. The duration of the total cold ischemic time was significantly related to both the duration of the plateau in morphine concentration ($P = 0.008$) and the first postoperative day creatinine clearance ($P = 0.021$). Morphine elimination half-life after the plateau was related to first postoperative day creatinine clearance ($P < 0.001$). It was concluded that morphine elimination depended upon intact renal function.*

Key Words: ANALGESICS—morphine. PHARMACOKINETICS—morphine.

A number of reports have indicated that morphine has greater effect in patients with renal dysfunction (1–4). Recent publications that have examined the kinetics of morphine and its congeners in renal failure (2,5–9) have, with one exception (10), concluded that the kidney has an important role in morphine elimination, although the mechanism remains obscure. Both kinetic (11) and biochemical (12) evidence suggest that the liver is unlikely to be involved in morphine removal from plasma, except at high plasma concentrations (13).

Previous studies (5) of morphine kinetics during and after renal transplant operations showed that plasma morphine concentrations decreased to a plateau between 500 and 1000 nmol/L soon after bolus intravenous injection. The plateau phase ended when the transplanted kidney began to function after the period of cold ischemia. The previous study was conducted mainly on patients receiving transplants from living-related donors, where the cold ischemic time was relatively short; it suggested that different conditions applied to operations using transplanted kidneys from cadavers, where cold ischemic times may be prolonged.

This study compared morphine plasma concentrations in 15 patients undergoing renal transplantation with kidneys from either living-related donors or cadavers. At the start of the procedure the patients have no functioning renal tissue, but at some time afterwards they have a healthy, functioning kidney. The effect of a rapid reversal of pathophysiology on morphine kinetics can thus be safely and ethically studied in such patients. The effects of differences in the total cold ischemic time (TCIT) before renal revascularization on both morphine kinetics and the functioning of the transplanted kidney over the first postoperative day were examined.

## Patients and Methods

Patients undergoing renal transplantation gave informed consent, and the study was approved by the local hospital ethics committee. All patients were suffering from end-stage renal failure and were receiving treatment by either hemodialysis or continuous am-

---

Received from the Nuffield Departments of Anaesthetics and Clinical Biochemistry, Radcliffe Infirmary, Oxford; Nuffield Department of Surgery, John Radcliffe Hospital, Oxford; and Renal Unit, Churchill Hospital, Oxford, United Kingdom. Accepted for publication May 9, 1985.

Address correspondence to Dr. Moore, Nuffield Department of Clinical Biochemistry, Radcliffe Infirmary, Oxford OX2 6HE, United Kingdom.

No reprints will be available from the authors.

© 1985 by the International Anesthesia Research Society

bulatory peritoneal dialysis; patients were dialyzed within 12 hr of the start of anesthesia. Four of the patients were insulin-dependent diabetics who received a pancreatic transplant during the same operation as the renal graft. Six patients (four receiving kidneys from living-related donors, two receiving cadaveric grafts) were receiving antihypertensive therapy (either vasodilators or $\beta$-adrenergic blocking drugs).

Patients were premedicated with 10–15 mg oral diazepam 2 hr before surgery. Anesthesia was induced with thiopental, 4 mg/kg, and the trachea was intubated after neuromuscular relaxation with *d*-tubocurarine, 0.5 mg/kg, or vecuronium, 0.1 mg/kg. Maintenance of anesthesia was with 60% nitrous oxide in oxygen, supplemented with halothane (less than 0.5%) or enflurane (less than 0.2%). Ventilation was to normocapnia using the Bain circuit with a fresh gas flow of 70 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and a tidal volume of 10 ml/kg.

After induction, when blood pressure and heart rate were stable, a single dose of 10 or 20 mg morphine sulphate pentahydrate (diluted to 10 ml with 0.154 mol/L saline) was injected into a flowing peripheral infusion over 20 sec. All sample times were taken from the end of the injection. Central venous samples (1 ml) were collected at regular intervals to 3 hr, and then as appropriate to 1440 min (24 hr). Blood was collected into tubes containing lithium heparin anticoagulant, and the plasma was separated by centrifugation and stored frozen until analysis.

During the operation 0.154 mol/L saline was infused at 10–20 $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, sufficient to increase the central venous pressure to 10–12 cm water by the time of renal revascularization. The diabetic patients also received intravenous dextrose and insulin as appropriate to maintain blood glucose concentrations of 8–10 mmol/L.

Renal transplantation was performed through a loin incision with the donor graft anastomosed extraperitoneally to the iliac vessels. In the four diabetic patients, the pancreatic graft was placed intraperitoneally in the opposite iliac fossa. TCIT was defined as the time from cessation of perfusion of the donated kidney to the time of release of the vascular clamps in the recipient.

At the end of surgery, neuromuscular blockade was reversed with atropine, 1.2 mg, and neostigmine, 2.5 mg, intravenously, and the patients breathed 28% oxygen via face mask for 12 hr. Postoperative analgesia was provided by 50–75 mg intramuscular meperidine as required.

Plasma morphine concentrations were measured by specific radioimmunoassay (14), and plasma and urine creatinine using the IL 919 analyzer. Creatinine clearance was calculated for the first postoperative day using a 24-hr collection of urine, commencing at the end of surgery. The area under the concentration–time curve for 24 hr after morphine injection ($\text{AUC}_{0-24}$) was calculated by the trapezoidal rule and plasma clearance of morphine calculated by division of the dose by $\text{AUC}_{0-24}$. The terminal half-life of morphine was determined by linear regression analysis using sample points after the plateau phase. The duration of the plateau phase was defined as the interval between the time of morphine injection and the time of the first sample that had a morphine concentration lower (by more than twice the coefficient of variation of the assay) than the plateau concentration.

Table 1. Demographic Variables

| | Kidney Origin | |
|---|---|---|
| | Living-Related ($n$ = 6) | Cadaver ($n$ = 9) |
| Age (yr) | 33.5 ± 5.7 | 37.7 ± 3.6 |
| Weight (kg) | 60.5 ± 7.5 | 67.3 ± 4.3 |
| Urea (mmol/L) | 19.6 ± 2.9 | 18.1 ± 2.5 |
| Creatinine ($\mu$mol/L) | 742 ± 81 | 836 ± 74 |
| Albumin (g/L) | 40.2 ± 2.4 | 41.4 ± 1.3 |
| Total protein (g/L) | 67.3 ± 3.6 | 70.7 ± 2.1 |
| Aspartate transaminase (mU/L) | 17.7 ± 2.5 | 16.0 ± 4.2 |
| Hemoglobin (g/dl) | 7.5 ± 0.7 | 9.4 ± 0.6 |

There were no significant differences between the two patient groups using the Mann–Whitney *U*-test.

The ability of human whole heparinized blood or heparinized plasma to hydrolyze morphine-3-glucuronide was tested. Plasma samples obtained from a healthy male volunteer were incubated with 200, 2000, or 20,000 nmol/L of morphine-3-glucuronide (Sigma, Poole, Dorset) at 37°C for up to 5 hr with and without addition of $\beta$-glucuronidase ($\beta$-D-glucuronide glucuronohydrolase, EC.3.2.1.31, Type VII from *Escherichia coli*, Sigma, London). Samples were removed before the incubation commenced, and at various times thereafter for morphine assay (14). Mean data are quoted throughout, together with the standard error of the mean (SEM). Statistical analysis was with the Mann–Whitney *U*-test, paired *t*-test, or correlation analysis, as appropriate.

## Results

The demographic details of the 15 patients studied are shown in Table 1 for patients receiving a transplanted kidney from a living-related donor ($n$ = 6) or a cadaver ($n$ = 9). There were no preoperative biochemical or hematologic differences between the two subgroups. The mean values for TCIT for transplanted kidney from living-related donors was 113

Table 2. Plasma Morphine Concentrations during the First 3 hr

| | Kidney Origin | |
|---|---|---|
| Time (min) | Living-Related ($n$ = 6) (nmol·L$^{-1}$·mg$^{-1}$) | Cadaver ($n$ = 9) (nmol·L$^{-1}$·mg$^{-1}$) |
| 1 | 226 ± 94 | 286 ± 250 |
| 2 | 113 ± 20 | 128 ± 60 |
| 5 | 48 ± 2.5 | 49 ± 18 |
| 10 | 38 ± 11 | 37 ± 18 |
| 15 | 41 ± 7.2 | 33 ± 17 |
| 20 | 39 ± 11 | 34 ± 18 |
| 30 | 44 ± 10 | 34 ± 15 |
| 60 | 46 ± 4.0 | 38 ± 12 |
| 90 | 49 ± 4.2 | 41 ± 12 |
| 120 | 49 ± 4.0 | 38 ± 11 |
| 150 | 47 ± 4.6 | 40 ± 10 |
| 180 | 44 ± 2.7 | 37 ± 3.6 |

There were no significant differences between the two patient groups using the Mann–Whitney *U*-test. There was no significant change in plasma morphine concentrations between 15 and 180 min in either patient group (paired *t*-test).

min, significantly shorter than the mean TCIT of 832 min for kidneys from cadavers ($P < 0.01$).

During the first 3 hr after the dose of morphine, and before the transplanted kidneys began to clear creatinine, there were no statistically significant differences between plasma morphine concentrations for the two groups of patients (Table 2). In both groups there was a rapid initial decline in plasma morphine concentrations, followed by a plateau phase during which no further decline occurred. There were no significant changes in plasma morphine concentrations between 15 min and 180 min in either group (paired *t*-test, Table 2).

This plateau phase, found in all the patients, was at plasma morphine concentrations between 250 and 1300 nmol/L. The duration was longer in the patients receiving kidneys from cadavers (Table 3; Figs. 1, 2). The duration of the plateau phase was significantly shorter in patients receiving a kidney from a living-related donor (417 ± 53 min) than in those whose transplanted kidney was from a cadaver (847 ± 99 min; Table 3, $P < 0.01$, Mann–Whitney *U*-test). There was a significant correlation between duration of the plateau and TCIT ($r = 0.83$, $P = 0.008$, $n = 15$, Fig. 3).

Plasma morphine concentrations began to decline after the plateau phase in all patients. The rate of decline was faster in patients who received a transplanted kidney from a living-related donor (Fig. 1, Table 3), than in those who received a transplanted kidney from a cadaver (Fig. 2). Thus the mean terminal half-life for morphine was significantly shorter in those receiving transplanted kidney from a living-related donor (284 ± 31, compared with 604 ± 132 min, $P < 0.01$, Mann–Whitney *U*-test, Table 3). Correspondingly, morphine clearance was significantly greater in patients receiving a transplanted kidney from a living-related donor (107 ± 8 compared with 81 ± 8 ml/min, $P < 0.01$, Table 3).

Table 3. Relationship of Morphine Kinetics and First-Day Renal Function to Total Cold Ischemic Time

| | Kidney Origin | |
|---|---|---|
| | Living-Related | Cadaver |
| TCIT (min) | 113 ± 20 | 832 ± 154[a] |
| Morphine elimination half-life (min) | 284 ± 31 | 604 ± 132[a] |
| Duration of plateau (min) | 417 ± 53 | 847 ± 99[a] |
| Morphine clearance (ml/min) | 107 ± 8 | 81 ± 8[a] |
| First-day creatinine clearance (ml/min) | 112 ± 23 | 43 ± 12[a] |

[a] There was a significant difference ($p < 0.01$, Mann–Whitney *U*-test) between the two groups of patients for each of these parameters.

Postoperative renal function was also different in the two patient groups. Over the first 24 hr after surgery the creatinine clearance was significantly higher in patients receiving a transplanted kidney from a living-related donor (112 ± 23 compared to 43 ± 12 ml/min, $P < 0.01$, Table 3). In 12 of the 15 patients, plasma creatinine concentrations were also measured on each plasma sample during the 24-hr period after intravenous morphine. In each case there was a plateau in plasma creatinine for 4–15 hr, and then an abrupt decrease occurred. In each patient the sample point at which plasma morphine began to decrease was that at which plasma creatinine also began to decrease (a significant change being defined as more than twice the intraassay coefficient of variation at that concentration).

Morphine elimination could be related to postoperative renal function. There was a significant curvilinear exponential relationship between terminal morphine half-life in plasma and first day creatinine clearance (half-life = 2450 × creatinine clearance$^{-0.47}$, $r = 0.93$, $P < 0.001$, Fig. 4). In addition there were significant linear correlations between TCIT and creatinine clearance ($r = -0.59$, $P = 0.021$) and TCIT and morphine clearance ($r = -0.59$, $P = 0.022$). No relationships were found between morphine disposition and any other preoperative biochemical or hematologic parameters.

Incubation of human plasma, serum or whole heparinized blood with morphine-3-glucuronide at concentrations of approximately 200, 2000, or 20,000 nmol/L

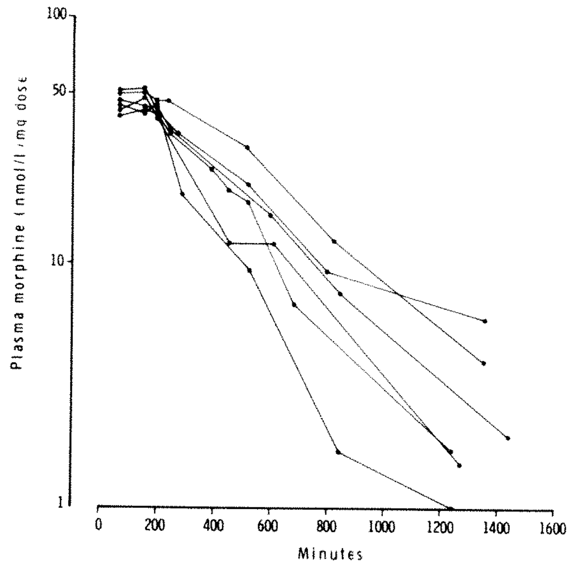


Figure 1. Plasma morphine concentrations in individual patients receiving a transplanted kidney from a living-related donor.

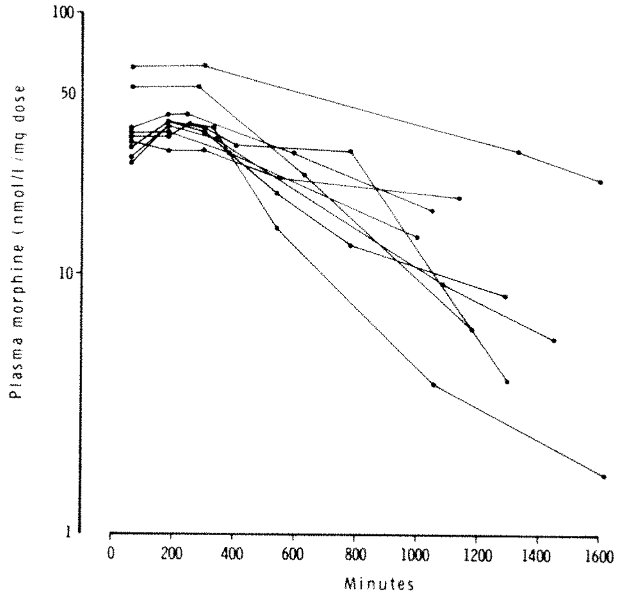


Figure 2. Plasma morphine concentrations in individual patients receiving a transplanted kidney from a cadaver.

produced no measurable deglucuronidation to morphine in incubations at 37°C for up to 5 hr. Addition of $\beta$-glucuronidase resulted in substantial production of morphine in both whole blood and plasma.

## Discussion

The data presented here confirm and extend previous observations on the unusual nature of morphine plasma concentrations in renal transplant patients (5), and they concentrate on the differences between patients receiving kidney grafts of living-related or cadaveric origin.

Renal function in the first postoperative day was very different depending on whether the kidney came from a living-related donor or from a cadaver. All kidneys, whether of cadaveric origin or from a living relative, were taken from beating-heart donors. The warm ischemic time was, therefore, short (less than 2 min). The TCIT was considerably longer in the kidneys of cadaveric origin than those from a living-related donor; longer TCIT is known to result in more extensive damage to the transplanted kidney, which then takes longer to recover (15). The finding that first-day creatinine clearance was significantly reduced if the transplanted kidney was of cadaveric origin (Table 3) was, therefore, not surprising. Transplanted kidneys from living-related donors gave normal first-day creatinine clearance because the transplanted kidney began to function early, some 3–6 hr after the recipient had been given morphine.

The initial 3 hr after the recipients had been given morphine was while they were still anephric, whether the transplanted kidney was of living-related or cadaveric origin. No difference in plasma morphine concentrations between the groups was, therefore, predicted during this period, and none was found (Table 2). In the absence of a functioning kidney, morphine plasma concentrations did not decline after the initial distribution phase, indicating that no significant morphine elimination occurred in the absence of functioning renal tissue. As liver function tests were quite normal in these patients (Table 1), the implication was that the liver did not eliminate morphine at these plasma morphine concentrations, which is in accord with the known kinetics of morphine in patients with moderate to severe cirrhosis given similar intravenous doses (11).

Plasma creatinine was monitored in 12 patients; this also showed a plateau followed by a rapid decrease in plasma creatinine concentrations in the postoperative period, indicating the return of renal filtration function after the period of cold ischemia. In each case the sample in which plasma creatinine began to decrease was the sample in which plasma morphine also began to decrease, indicating that morphine elimination was also dependent upon the return of renal filtration function (5).

The plateau phase in morphine plasma concentrations was relatively short in patients receiving kidneys from living-related donors (Fig. 1), but was much longer in those receiving kidneys from cadavers (Fig. 2). Because the end of the plateau phase in individual patients was related to the return of the renal filtration

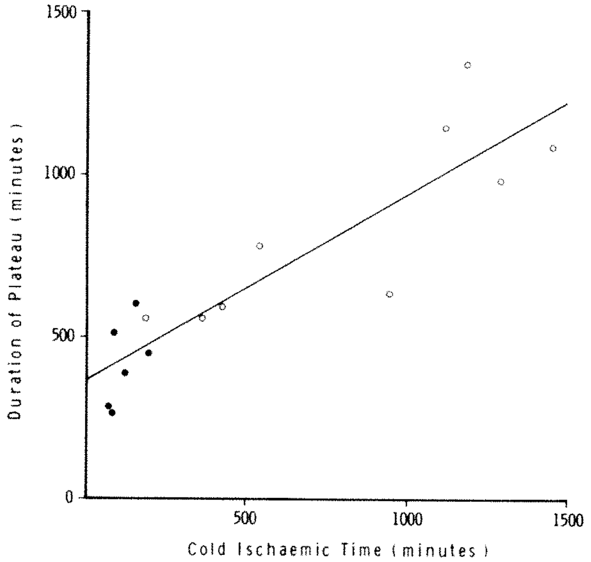


Figure 3. Relationship between TCIT and duration of morphine plateau ($r = 0.83$, $P = 0.008$). Origin of transplanted kidneys was living-related (closed circle) and cadaveric (open circle).

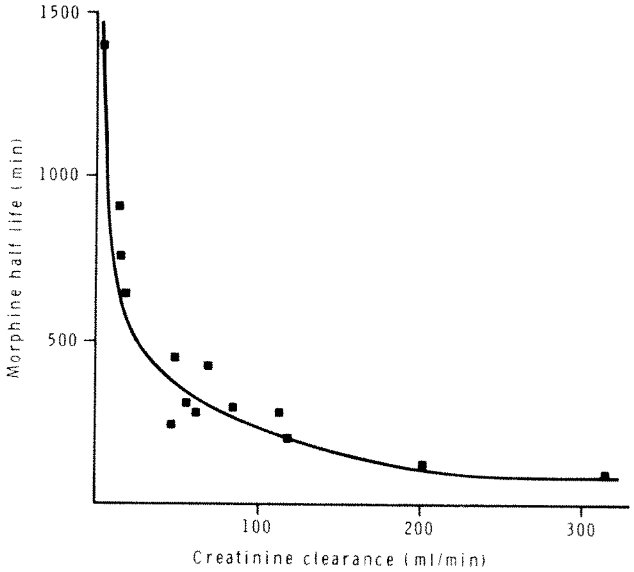


Figure 4. Relationship between morphine elimination half-life and first-day creatinine clearance ($r = 0.93$, $P < 0.001$).

function, the good correlation between the duration of the plateau phase in morphine concentrations the TCIT (Fig. 3) was expected. What was surprising was that the pretransplant condition of the transplanted kidney had such a major effect on morphine kinetics in the recipient. The only possible explanation of a relationship between TCIT and morphine disposition kinetics must be that TCIT determined the behavior of the transplanted kidney in the immediate postoperative period, and that in turn the functional ability of the transplanted kidney influenced morphine disposition kinetics.

The large extra contribution of the plateau phase to the area under the concentration–time curve explains why systemic morphine clearance in patients receiving a transplanted kidney from a cadaver was less than in those receiving a kidney from a living-related donor. The plateau also explains why morphine clearance was less than that found previously in control patients with normal renal function if no plateau was observed (5). The elimination half-life of morphine in the patients receiving a transplanted kidney from a living-related donor was not dissimilar to that found in other studies (14); these patients had normal renal function early on the first day. For patients receiving a transplanted kidney from a cadaver, where return to normal function was delayed, the elimination half-life of about 10 hr was prolonged.

Overall, the relationship between the morphine elimination half-life and first-day creatinine clearance was excellent (Fig. 4) and is similar to relationships described for drugs eliminated mainly by the kidney (16). Significant relationships have also been found between morphine clearance and creatinine clearance in patients with normal (2) and abnormal (6) renal function. A morphine elimination half-life of 73 hr has been reported for one patient with end-stage renal failure (7). In another study (10) no prolongation of half-life was found for morphine in patients with renal failure. However, the duration of sampling was only 2 hr, which precluded the accurate estimation of a long elimination half-life (17). This is especially important as the study was designed to measure potential prolongation of elimination half-life in renal failure.

The major metabolic fate of morphine is glucuronidation to morphine-3-glucuronide, which is then excreted in the urine. One possible explanation of the results presented here, and especially of the plateau in plasma morphine concentrations, would be if the accumulation of morphine-3-glucuronide in blood resulted in hydrolysis of the glucuronide back to morphine because of renal insufficiency. The demonstration that this did not occur even at extremely high concentrations refutes this explanation and is in accord with the finding that hydrolysis of morphine glucuronide does not occur in uremia (18).

The results here do not constitute evidence that the normal or transplanted kidney is capable of either the glomerular filtration or tubular secretion of morphine, or of its metabolites if morphine metabolism occurs within the renal parenchyma. However, the relationship found between morphine elimination half-life and creatinine clearance (Fig. 4) is exactly the same as the theoretical calculation of the effect of changing renal function on morphine elimination, assuming that renal excretion is the only mechanism of elimination (4). Moreover, in the rabbit kidney isolated tubule segments have been shown to accumulate and glucuronidate morphine at concentrations typically found after therapeutic doses in man (19). Intact renal function may be important for the efficient elimination of morphine congeners, such as dihydrocodeine (8,9), as well as for morphine.

There is little evidence for substantial hepatic involvement in morphine metabolism in humans. In cirrhosis, which is known to reduce the systemic clearance of pentazocine and meperidine (20), there was no effect on morphine clearance (11). Drugs that reduce hepatic blood flow (cimetidine and propranolol) had no effect on morphine kinetics (21,22). Moreover, the hepatic microsomal enzymes presumed to be responsible for morphine glucuronidation had a $K_m$ for morphine several orders of magnitude above therapeutic concentrations of morphine in plasma (23).

Even though there is a lack of understanding about the mechanism by which morphine removal is altered in patients with renal failure, there is considerable circumstantial evidence that it has important clinical sequelae. Prolonged narcosis has been reported after a single-bolus dose of morphine in patients with uremia (1), and there are numerous case reports of unexpectedly profound and prolonged respiratory depression after morphine administration to patients with renal problems (2). Cancer pain patients allowed to titrate themselves to analgesia needed only one-fourth of the average dose when they had increased plasma creatinine concentrations (3).

What does this mean for patients with renal failure about to undergo surgery? The perioperative administration of morphine (and probably diamorphine, codeine, and dihydrocodeine) should be carefully considered in anticipation of a greater degree and duration of effect and side effect for a given dose. Postoperative analgesia for these patients should never be by fixed dose schedules with drugs of the morphine family. Individual titration of dose to requirement by patient-demand techniques may well be the ideal.

## References

1. Don HF, Dieppa RA, Taylor P. Narcotic analgesics in anuric patients. Anesthesiology 1975;42:745–7.
2. McQuay HJ, Moore RA. Be aware of renal function when prescribing morphine. Lancet 1984;ii:284–5.
3. Regnard C, Twycross RG. Metabolism of narcotics. Br Med J 1984;288:860.
4. Mostert JW, Evers JL, Hobika JH, Moore RH, Ambrus JL. Cardiorespiratory effects of anaesthesia with morphine or fentanyl in chronic renal failure and cerebral toxicity after morphine. Br J Anaesth 1971;43:1053–60.
5. Moore RA, Sear J, Baldwin D, Allen MC, Hunniset A, Bullingham RES, McQuay HJ. Morphine kinetics during and after renal transplantation. Clin Pharmacol Ther 1984;35:641–5.
6. Ball M, McQuay HJ, Moore RA, Allen MC, Fisher A, Sear J. Renal failure and the use of morphine in intensive care. Lancet 1985;i:784–6.
7. Michie CE, Chapman JR, Sear J, Moore RA. Opioid metabolism and the kidney. Lancet 1985;1:586.
8. Barnes JN, Williams AJ, Toseland PA, Goodwin FJ. Opioid drugs and renal failure. Lancet 1984;2:748.
9. Barnes JN, Williams AJ, Tomson MJF, Toseland PA, Goodwin FJ. Dihydrocodeine in renal failure: further evidence for an important role of the kidney in the handling of opioid drugs. Br Med J 1985;290:740–2.
10. Aitkenhead AR, Vater M, Achola K, Cooper CMS, Smith G. Pharmacokinetics of single-dose I.V. morphine in normal volunteers and patients with end-stage renal failure. Br J Anaesth 1984;56:813–9.
11. Patwardhan RV, Johnson RF, Hoyumpa A, Sheehan JJ, Desmond PV, Wilkinson G, Branch RA, Schenker S. Normal metabolism of morphine in cirrhosis. Gastroenterology 1981;81:1006–11.
12. Iwamoto K, Eaton DL, Klaassen CD. Uptake of morphine and nalorphine by isolated rat hepatocytes. J Pharmacol Exp Ther 1978;206:181–9.
13. Bullingham RES, Moore RA, Symonds HW, Allen MC, Baldwin D, McQuay HJ. A novel form of dependency of hepatic extraction ratio of opioids upon the portal vein concentration of drug: comparison of morphine, diamorphine, fentanyl, methadone and buprenorphine in the chronically cannulated cow. Life Sci 1984;34:2047–56.
14. Moore RA, Baldwin D, Allen MC, Watson PJQ, Bullingham RES, McQuay HJ. Sensitive and specific morphine radioimmunoassay with iodine label: pharmacokinetics of morphine in man after intravenous administration. Ann Clin Biochem 1984;21:318–25.
15. Marshall VC. Renal preservation. In: Morris, ed. Kidney transplantation, principles and practice. London: Cruse & Stratton, 1984:129–57.
16. Welding PG, Craig WA. Pharmacokinetics in disease states modifying renal function. In: Benet LZ, ed. The effect of disease states on drug pharmacokinetics. Washington, DC: American Pharmaceutical Association Center, 1976:155–87.
17. Reidenberg MM. In: Foley K, Inturrisi CE, eds. Opioids in the management of clinical pain. New York: Raven Press, in press.
18. Bullingham RES, McQuay HJ, Porter EJB, Thomas D, Allen MC, Moore RA. Acute I.V. methadone kinetics in man: relationship to chronic studies. Br J Anaesth 1982;54:1271–6.
19. Schali C, Roch-Ramel F. Transport and metabolism of [3H]morphine in isolated, nonperfused proximal tubular segments of the rabbit kidney. J Pharmacol Exper Ther 1982;223:811–5.
20. Neal EA, Meffin PJ, Gregory PB, Blashke TF. Enhanced bioavailability and decreased clearance of analgesics in patients with cirrhosis. Gastroenterology 1979;77:96–102.
21. Brunk SF, Delle M, Wilson WR. Effect of propranolol on morphine kinetics. Clin Pharmacol Ther 1975;16:1039–44.
22. Mojavarian P, Fedder IL, Vlasses PH, Rotmensch HH, Rocci ML, Swanson B, Ferguson R. Cimetidine does not alter morphine disposition in man. Br J Clin Pharmacol 1982;14:809–13.
23. Sawe J, Pacifici GM, Kager L, von Bahr C, Rane A. Glucuronidation of morphine in human liver and interaction with oxazepam. Acta Anaesthesiol Scand 1982;(supp 74):47–51.

# Effects of Glycine on Hemodynamic Responses and Visual Evoked Potentials in the Dog

Janice Mei-li Wang, MD, K. C. Wong, MD, PhD, Donnell J. Creel, PhD, W. Matt Clark, MD, and Shahram Shahangian, PhD

WANG JM, WONG KC, CREEL DJ, CLARK WM, SHAHANGIAN S. Effects of glycine on hemodynamic responses and visual evoked potentials in the dog. Anesth Analg 1985;64:1071–7.

*To study the potential contribution of glycine toxicity in the transurethral resection syndrome, we evaluated hemodynamic and visual evoked potential responses to glycine infusion (1 g/kg) in 22 dogs anesthetized with halothane (1.0–1.2% end tidal). Three dogs received 5% glucose in normal saline without glycine; three received arginine (4 mg/kg) in normal saline without glycine; three received arginine (4 mg/kg) in normal saline without glycine; 10 received glycine (1 g/kg), then arginine (4 mg/kg) 120 min after the completion of glycine infusion; and six received arginine 30 min after the completion of glycine infusion. Arginine was infused to evaluate potential antagonistic effects of glycine toxicity. Blood levels of glycine, ammonia, arginine, urea, and formate were determined after infusions of glycine or arginine. All animals received about 5* $ml{\cdot}kg^{-1}{\cdot}hr^{-1}$ *of normal saline during the 2–4 hr of study. Immediately after glycine infusion, cardiac output increased 57%, whereas systemic vascular resistance and mean arterial pressure decreased 32% and 8%, respectively. Later cardiac output and mean arterial pressure were 41% and 18% less than control levels, whereas systemic vascular resistance returned to control levels. Both amplitude and latency of visual evoked potential waveforms were altered in the animals receiving glycine infusion but not in the control animals. These responses were associated with elevations of blood glycine (149 ± 5 to 9591 ± 809 μM/L, mean + SEM) and blood* $NH_3$ *(10.5 ± 2.8 to 100.0 ± 13.6 μM/L), but not with formate levels. Infusion of arginine 30 min after the completion of glycine infusion was associated with a reduction of blood glycine levels, but not more than that accountable by the effect of time. Arginine infusion alone in halothane-anesthetized dogs produced no hemodynamic or visual evoked potential waveform changes. However, in the presence of elevated blood glycine and ammonia levels, arginine improved cardiac output and minimized visual evoked potential waveform changes. These results suggest that chemical toxicity from glycine absorption, in addition to water intoxication and hyponatremia, should be considered in the "transurethral resection of the prostate syndrome."*

Key Words: SURGERY, UROLOGIC—transurethral prostatectomy. TOXICITY—glycine, ammonia.

Untoward side effects of transurethral resection of the prostate (TURP) were noted over 30 yr ago (1). Since then, a range of complications associated with this procedure has been described. Some patients manifest predominantly visual difficulties (2,3), others manifest excessive sedation and difficult emergence from anesthesia (4,5), and still others manifest cardiovascular instability and even collapse (6,7). In the past this "TURP syndrome"—cardiopulmonary difficulties, central nervous system (CNS) aberrations, visual disturbances, and coma—has been attributed to excessive intravascular absorption of irrigating solution through prostatic sinuses and veins resulting in fluid overload and hyponatremia. Recently, however, glycine, the osmolar component of the surgical irrigant, and its metabolite, ammonia, have been implicated in the pathogenesis of the TURP syndrome. Serum levels of both substances have been found to be elevated postoperativly in patients who manifest features of the TURP syndrome (2,4,5).

Many characteristics of glycine make it a likely cause of the syndrome. It is an inhibitory neurotransmitter in the CNS, retina, and spinal cord (8). High glycine levels are suspected of causing abnormal electroen-

---

Supported in part by the Medical Research Service of the Veterans Administration Hospital and the Utah Anesthesia Research Foundation. A portion of this paper was presented at the ASA meeting in New Orleans, Louisiana, October 1984.

Received from the Departments of Anesthesiology and Ophthalmology, University of Utah School of Medicine and the VA Medical Center, Salt Lake City, Utah. Accepted for publication June 3, 1985.

Address correspondence to Dr. Wong, Department of Anesthesiology, University of Utah School of Medicine, 50 North Medical Drive, Salt Lake City, UT 84132.

© 1985 by the International Anesthesia Research Society

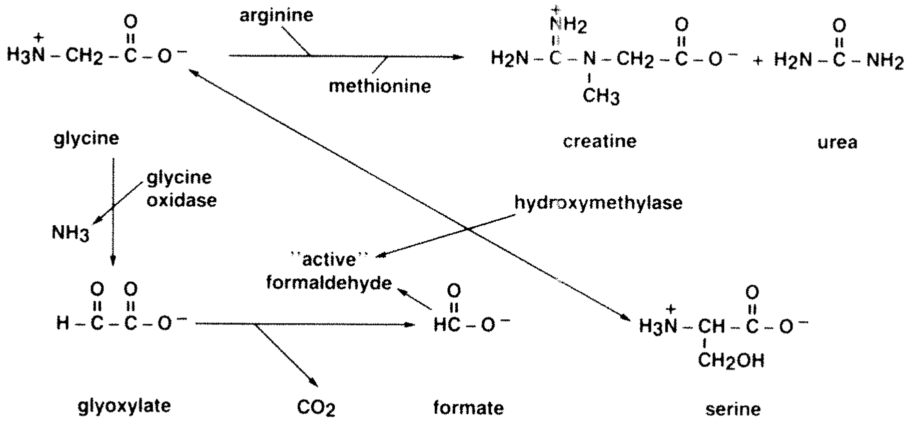


Figure 1. Glycine biochemistry simplified. Deamination and decarboxylation of glycine produce potentially harmful metabolites ammonia, formate, and formaldehyde. The reaction from glycine to serine is reversible with the formation or utilization of formic acid products. Glycine reacts with substrates arginine and methionine to form creatine and urea.

cephalographic activity as well as abnormal visual and auditory evoked responses in patients with congenital nonketotic hyperglycinemia (9). Furthermore, when large quantities of glycine are injected intravitreously into the eyes of a rabbit, there is suppression of waveforms of both the electroretinogram and visual evoked potentials (VEPs) (10). Both ammonia and formate are products of glycine metabolism (Fig. 1) (11) and are known to produce CNS toxicity. Arginine, a substrate for the metabolism of glycine (11), has been shown to reduce the formulation of ammonia from glycine metabolism (12,13).

The present study was undertaken to study trends in the hemodynamic responses and waveforms of VEPs in dogs after intravenous infusion of glycine comparable to amounts that could be absorbed in humans during a TURP (2). These were correlated with blood levels of glycine, ammonia, formate, and urea. Arginine was also infused to evaluate possible influence on glycine metabolism, glycine-induced hemodynamic effects, and VEP waveforms.

## Methods

Twenty-two mongrel dogs, 15–25 kg, were anesthetized with halothane (1.0–1.2% end tidal) in oxygen after thiopental (10–15 mg/kg intravenously) induction. After endotracheal intubation, the lungs were mechanically ventilated to maintain $P_{CO_2}$ between 30 and 35 mm Hg (normal for Salt Lake City, UT elevation 4500 feet above sea level) without the administration of muscle relaxants. A pulmonary artery catheter with thermodilution cardiac output was placed surgically through the external jugular vein. After 30–45 min for stabilization, the following groups of animals were studied: group 1, three control animals receiving 5% glucose intravenously in normal saline (5 $ml \cdot kg^{-1} \cdot hr^{-1}$) without glycine; group 2, three control animals receiving arginine HCl 10% (4 mg/kg) in 200 ml normal saline, infused over 20 min without glycine; group 3, 10 animals receiving intravenous glycine, 1 gm/kg, dissolved in 200 ml of normal saline over 20 min, and then 120 min after the infusion of glycine 10% arginine HCl intravenously (4 mg/kg) over 20 min. Group 4 consisted of six animals receiving intravenous glycine, as in group 3, but the intravenous arginine was infused immediately after glycine. All 22 animals received approximately 5 $ml \cdot kg^{-1} \cdot hr^{-1}$ of normal saline during the course of the study period. Visual evoked potential (VEP), heart rate (HR), mean arterial pressure (MAP), cardiac output (CO), right arterial pressure (RAP), pulmonary artery pressure (PAP), pulmonary artery wedge pressure (PAWP), and arterial blood gas (ABG) were recorded every 60 min in all groups, and immediately before and after the infusion of glycine or arginine. Systemic vascular resistance was calculated in the usual manner. Blood levels of glycine, ammonia, arginine, urea, and formate determined in four animals of group 3 and in all six animals of group 4, were performed by standard methods of The University of Utah Clinical Laboratory.

Visual evoked potentials were recorded from occipital locations with subdermal needle electrodes. The reference electrode was inserted into the rostral attachment of the pinna, and the ground electrode into a leg. After the dog was stabilized on halothane–oxygen and prior to the infusion of glycine, multiple occipital locations were explored to find the most reliable location for recording VEPs. The lamp of a Grass PS22 photostimulator was placed 20 cm from the eyes of the dog. Single flashes were presented at the rate of one flash per second. Responses to 61 flashes were averaged to form the VEP. At least four VEPs were recorded to test reliability. The best waveform of maximum amplitude was selected from the four for statistical analyses. Peak latencies and peak-to-peak amplitudes were measured using the cursors on a Nicolet CA-2000 computer oscilloscope

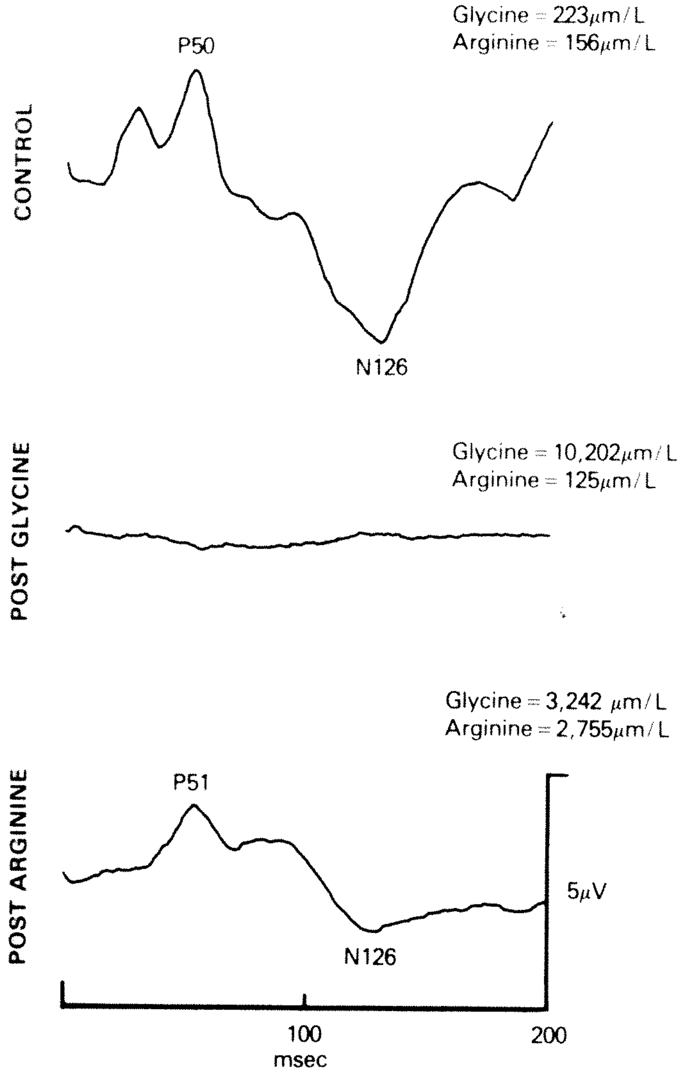


Figure 2. Representative visually evoked potentials recorded from a dog dramatically affected by glycine infusion (1 g·kg$^{-1}$·20 min$^{-1}$) and later arginine infusion (4 mg·kg$^{-1}$·20 min$^{-1}$). Vertical calibration, 5 μV.

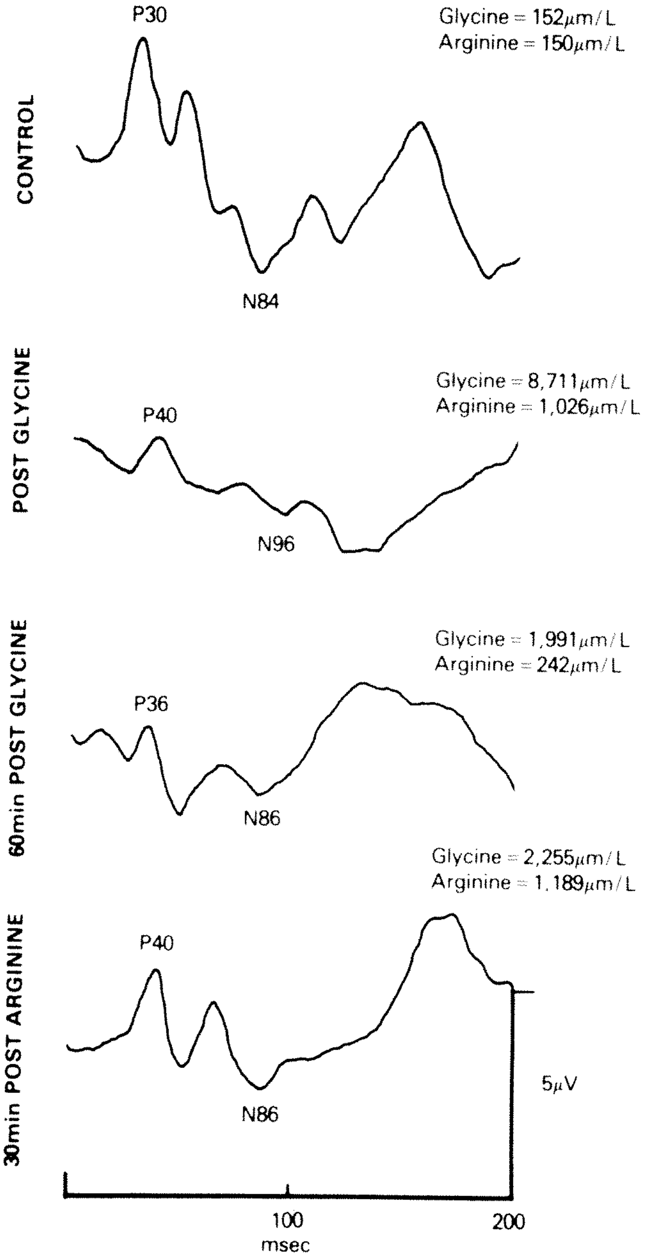


Figure 3. Representative visually evoked potentials recorded from a dog following glycine infusion (1 g·kg$^{-1}$·20 min$^{-1}$) and later arginine infusion (4 mg·kg$^{-1}$·20 min$^{-1}$). In panel 2, the elevated level of arginine occurred after glycine infusion was associated with the presence of VEP waveform (in contrast to Fig. 2, panel 2). In panel 4, there was further restoration of VEP waveform after arginine infusion. Vertical calibration, 5 μV.

display. The peak latency of the prominent positive component appearing between 40–50 msec in the VEP of most dogs and the amplitude of the largest negative component peaking at around 100 msec were analyzed statistically (Figs. 2, 3).

Another method used for measuring amplitude is "total excursion." By tracing the response pattern of the evoked potential with a map reading wheel for the extent of time of analysis, a numerical value results which reflects the total positive and negative amplitude excursion of the evoked potential (14). This number estimates the total voltage excursion of the evoked potential and is sometimes more reliable than measuring individual components, especially in studies such as this where components of the evoked potential sometimes completely drop out as in Figure 2. The same evoked potentials analyzed for "P50" peak latency and "N100" amplitude were measured with a map reading wheel to the nearest centimeter across the first 200 msec. On these plots 1 cm equalled approximately 1 μV.

Table 1. Hemodynamic Variables in Control Dogs Maintained on Halothane–$O_2$ ($n = 3$, mean ± SEM)

| | HR (beats/min) | MAP (mm Hg) | CO (L/min) | SVR (dyne · sec · $cm^{-5}$) |
|---|---|---|---|---|
| 0 min | 108 ± 6 | 97.0 ± 7.1 | 1.97 ± 0.09 | 3664 ± 210 |
| 60 min | 110 ± 7 | 95.0 ± 10.2 | 1.63 ± 0.10[a] | 4294 ± 594 |
| 120 min | 108 ± 9 | 96.3 ± 9.5 | 1.58 ± 0.11[a] | 4590 ± 796 |
| 180 min | 107 ± 10 | 97.3 ± 6.1 | 1.59 ± 0.11[a] | 4676 ± 661 |
| 240 min | 104 ± 10 | 94.3 ± 4.4 | 1.59 ± 0.10[a,b] | 4740 ± 492 |

[a] $P < 0.05$ as compared to control.
[b] $P < 0.05$ as compared to the same after glycine and arginine infusion (Table 2), unpaired $t$-test.

A two-way analysis of variance with repeated measurements on the second factor was performed on the latency and amplitude measurement of the VEPs. Analysis of variance for repeated measurements and paired and unpaired $t$-tests were used to analyze the hemodynamic and biochemical data. Statistical significance is considered at $P < 0.05$.

## Results

The results of the halothane-anesthetized control animals are shown in Table 1. Heart rate and MAP did not change substantially. Likewise, RAP, PAP, and PAWP did not change and therefore are not reported in Table 1. Cardiac output, however, decreased about 20% over the 4-hr period. This was accompanied by a slight increase in SVR that was statistically insignificant. VEP waveforms did not change. The infusion of arginine alone in three halothane-anesthetized animals, likewise, did not significantly alter the hemodynamic or VEP responses (similar to the control animals), therefore, the data are not displayed.

Hemodynamically, all dogs demonstrated an immediate response to glycine (Table 2). Cardiac output increased 57% over control values. This was accompanied by significant decreases in SVR (32%) and MAP (8%). Nevertheless, hemodynamic depression occurred in all subjects over time. CO and MAP deteriorated steadily, but the CO was transiently increased after the infusion of arginine. At the end of the experiment, 4 hr after administration of glycine and arginine, CO and MAP were 41% and 18% less than control levels, respectively. However, only the CO (Table 2) was significantly lower ($P < 0.05$) in comparison with the halothane anesthetized dogs (Table 1), i.e., 1.12 ± 0.10 vs 1.59 ± 0.10 L/min. The initial decrease in SVR after glycine was transient, and later values returned to control levels (Table 2).

End-tidal halothane concentrations were varied between 1.0 and 1.2%, adjusted by the depth of anesthesia monitored by overt movement of the animals. The variability of the waveforms of the VEPs was no greater when recordings were separated by an hour or more than among four reliability trials recorded within a 5-min period.

The VEPs were distinctly altered in all dogs after the infusion of glycine. The amplitude and latency of the principal waveform components of the VEP varied. The dog presented in Figure 2 showed complete extinction of the VEP waveform immediately after glycine infusion. Partial recovery, evidenced by improvement of amplitude to 50–75% of control values, was seen after infusion of arginine, when the glycine level was also substantially reduced. Seven out of 10 animals responded to glycine infusion with less severe VEP waveform changes as shown in Figure 3. The elevation of arginine levels is of significance in these seven animals before the administration of arginine (Figure 3, panel 2) in contrast to the three animals which did not exhibit increases in arginine levels (Figure 2, panel 2).

The analyses of variance indicated a significant difference ($P < 0.01$) between experimental and halothane-anesthetized control dogs for both peak latency of the component appearing around 40–45 msec ("P50") and amplitude of the negative component peaking around 100 msec ("N100"). In the glycine animals, the amplitude of "N100" was reduced from 4.2 ± 1.3 $\mu$V to 2.0 ± 0.7 $\mu$V ($P < 0.01$); in contrast, the amplitude of the "N100" component increased from 4.6 ± 2.1 $\mu$V to 6.7 ± 3.0 $\mu$V ($P > 0.1$) in the VEPs of the control animals. The peak latency of the "P50" component increased from 43.8 ± 10.7 msec to 55.2 ± 14.1 msec after glycine ($P < 0.01$). The peak latency of this component recorded from control dogs was 43.3 ± 10.7 msec to 43.8 ± 13.1 msec measured across the same time period without glycine.

The infusion of glycine was associated with concurrent increases in mean blood ammonia and arginine levels (Tables 3, 4). The elevated ammonia levels tend to be sustained over the course of this study, whereas both blood glycine and arginine levels showed

Table 2. Hemodynamic Effects after Glycine and Arginine Infusion ($n = 10$, mean ± SEM)

| | HR (beats/min) | MAP (mm Hg) | CO (L/min) | SVR (dyne · sec · cm$^{-5}$) |
|---|---|---|---|---|
| Baseline | 100 ± 5 | 107.1 ± 4.8 | 1.91 ± 0.14 | 4118 ± 494 |
| Immediately after glycine, 60 min after baseline | 101 ± 6 | 98.7 ± 5.0$^{a}$ | 3.00 ± 0.45$^{a}$ | 2813 ± 348$^{a}$ |
| 120 min after baseline | 95 ± 8 | 94.3 ± 4.8$^{a}$ | 1.50 ± 0.16$^{a}$ | 5056 ± 581 |
| Immediately after arginine, 80 min after baseline | 88 ± 5 | 92.7 ± 5.1$^{a}$ | 1.74 ± 0.18 | 4132 ± 387 |
| End, 240 min after baseline | 94 ± 10 | 87.4 ± 4.8$^{a}$ | 1.12 ± 0.10$^{a,b}$ | 6550 ± 972 |

[a] $P < 0.05$ as compared to control.

[b] $P < 0.05$ as compared to the same without glycine and arginine infusion (Table 1), unpaired *t*-test.

Table 3. Blood Levels of Glycine, Ammonia, Arginine, and Urea after Glycine and Arginine Infusion ($n = 6$, mean ± SEM)

| | Glycine ($\mu$M/L) | $NH_3$ ($\mu$M/L) | Arginine ($\mu$M/L) | Urea (mg/dl) |
|---|---|---|---|---|
| Baseline | 157 ± 14 | 7.8 ± 3.1 | 138 ± 14 | 15.1 ± 0.9 |
| Immediately after glycine, 60 min after baseline | 6843 ± 636 | 177.0 ± 46.1 | 890 ± 174 | 18.6 ± 2.2 |
| Immediately after arginine, 90 min after baseline | 3330 ± 590$^{a}$ | 170.3 ± 27.2 | 4112 ± 872$^{a}$ | 26.4 ± 1.8 |

All values are significantly different from respective baseline values, $P < 0.01$.

[a] $P < 0.01$ as compared with immediately after glycine values.

progressive decreases over time. The infusion of arginine did not increase the rate of decline of blood glycine above the fastest rate attributable to the effect of time (Tables 3, 4). There was a spontaneous 82% reduction of glycine levels 120 min after glycine administration (Table 4).

## Discussion

The biochemical pathways for glycine metabolism are illustrated in Figure 1 (11). An important pathway in glycine metabolism is its oxidative deamination by glycine oxidase to glyoxylate with the formation of ammonia, a potentially harmful metabolite. Glyoxylate undergoes further decarboxylation to form formate and formaldehyde. Thus another potentially harmful metabolite, formate, from glycine biotransformation can also contribute to visual disturbance (15,16). Finally, another alternative pathway of glycine metabolism is to utilize substrates arginine and methionine to form creatine and urea (Fig. 1). The choice of biochemical measurements made during this study is largely based upon this knowledge of glycine biotransformation.

We are not aware of any published data on the cardiovascular effects of glycine. Lethal doses of glycine in dogs produced vomiting and cardiovascular collapse (17). Our results suggest that there is an early augmentation of cardiac output associated with a concurrent reduction in MAP and SVR. A reduction in afterload could have improved cardiac output without a positive inotropic effect of glycine on the heart. Guertzenstein and Silver applied glycine to specific regions of the feline ventral medulla and observed a distinct decrease in arterial blood pressure (18), and they suggested that these vasomotor control areas were innervated by inhibitory neurons which released glycine. However, glycine also has been shown to inhibit spinal parasympathetic neurons in cats (19,20). A shifting of autonomic influence in favor of the sympathetic nervous system, especially $\beta$-adrenergic stimulation, would improve cardiovascular dynamics. The later cardiovascular depression observed in the present study is more difficult to explain. Because the RAP, PAP, and PAWP were not elevated after the glycine infusion, but CO and MAP were decreased, a direct myocardial depressant effect of glycine or glycine and halothane is a plausible explanation. Cardiovascular depression has been reported in the dog after glycine infusion (13,17,21) and in humans after absorption of glycine irrigating solution during TURP (4–7). Water intoxication, hyponatremia, and hyperammonemia have been the foci of discussion in these reports. Circulatory overload is not probable in the

Table 4. Blood Levels of Glycine, Ammonia, Arginine, and Urea after Glycine and Arginine Infusion ($n = 4$, mean ± SEM)

| | Glycine (μM/L) | $NH_3$ (μM/L) | Arginine (μM/L) | Urea (mg/dl) |
|---|---|---|---|---|
| Baseline | 149 ± 5 | 10.5 ± 2.8 | 124 ± 14 | 10.3 ± 1.7 |
| Immediately after glycine, 60 min after baseline | 9591 ± 809 | 100.0 ± 13.6 | 857 ± 162 | 17.0 ± 2.4 |
| 120 min after glycine | 1733 ± 314 | 115.5 ± 26.1 | 335 ± 100 | 20.3 ± 2.4 |
| Immediately after arginine, 180 min after baseline | 1779 ± 371 | 105.7 ± 33.5 | 4811 ± 1720 | 24.3 ± 2.9 |

Arginine was infused 2 hr after completion of the infusion of glycine, instead of immediately afterwards (Table 3).
All values are significantly different from respective baseline values, $P < 0.01$.

present study because of the normal RAPs and PAPs. We did not measure serum osmolarity or sodium levels because in our preliminary studies we found no changes in these measurements after glycine infusion; furthermore the volume of fluid administered was only about 5 $ml \cdot kg^{-1} \cdot hr^{-1}$ in all animals and always in the form of normal saline. Hyperammonemic cardiovascular depression, however, is a distinct possibility because blood ammonia levels remained elevated at above 100 μM/L (Tables 3,4) during the course of the study (baseline about 10 μM/L; and in humans 11–35 μM/L) (4).

Fahey, in 1957, described CNS toxic signs and marked increases in ammonia levels in dogs given intravenous amino acid mixture lacking L-arginine (12,13). The addition of arginine to the infusion reversed the increase in ammonia and the CNS toxicity. In the present study, neither the administration of arginine increased the rate of decline of glycine, nor reversed the rise of ammonia in the blood. But the period of observation after arginine infusion was limited to less than one hour (Tables 3, 4). However, the possibility exists that arginine may have a physiologic stabilizing effect on the cardiovascular system (Table 2) and VEPs (Figs. 2, 3) in the presence of elevated blood glycine and ammonia levels. It is not clear why there was an increase in blood arginine levels in some, but not all of the animals after glycine infusion, accounting for the large standard errors of mean arginine levels (Tables 3, 4). Although the infusion of arginine alone in three halothane-anesthetized dogs produced no cardiovascular or VEP changes, CO (Table 2) was transiently restored, and VEP waveforms were better maintained during elevated levels of blood arginine in the presence of elevated blood levels of glycine (Figs. 2, 3) and ammonia. These data support the observations of Fahey (12,13), but the mechanism of action of arginine remains obscure.

The measurement of VEPs is a useful method of quantitating visual disturbance in anesthetized animals and patients. We observed no changes in VEPs in the halothane-anesthetized control dogs. In surgical patients lightly anesthetized with halothane–$O_2$, Domino (23) reported minimal changes in VEPs with enhancement of secondary complexes, whereas Uhl et al. (24) observed dose-related increases in amplitudes and latencies of the waveforms from 0.75 to 1.13% end-expired levels of halothane. In the present study the amplitudes of VEP waveforms were significantly reduced, and the latencies were significantly prolonged during periods of high blood glycine levels. The role of glycine as a major inhibitory neurotransmitter of mammalian brain stem and spinal cord is well established, and more recent evidence suggests that this amino acid may also have a neurotransmitter role at supraspinal sites in the mammalian CNS (8). Glycine has been shown to inhibit ganglion cells in the retina (8), as well as to supress the waveforms of both the electroretinogram and VEP in rabbits (10,22). VEPs recorded from the occipital area reflect the entire process of visual reception involving the retina, optic nerve, lateral geniculate nucleus, optic radiations, and cortex. In a clinical setting, cerebral edema from water intoxication and abnormal nerve conduction from hyponatremia could also contribute to visual disturbance. Both glycine and ammonia levels were significantly elevated in the present study. However, the data favors glycine as the offending substance because the magnitude of peak glycine-increase was 43–64 times the baseline value and that of ammonia was 11–23 times that of baseline; and the decrease in glycine levels was associated with an improvement of VEP waveforms during which the ammonia levels still remained at peak-increase levels (Tables 3,4).

In summary, we have demonstrated the toxic effects of the infusion of glycine in amounts that could be absorbed during TURP in dogs. Metabolic products of glycine, ammonia, but not formate, were persistently elevated after glycine infusion. These chemical changes were associated with immediate deterioration of VEP waveforms and progressive decreases in CO and MAP. The infusion of arginine immediately or 2 hr after glycine did not alter the rate of decline of ammonia in the blood, but did improve CO and VEP waveforms. The results suggest that chemical toxicity, in addition to water intoxication and hyponatremia, should be considered in the "TURP syndrome."

## References

1. Creevy CD, Webb EA. Fatal hemolytic reaction following transurethral resection: a discussion of its prevention and treatment. Surgery 1947;21:56–66.
2. Ovassapian A, Joshi CW, Brunner EA. Visual disturbances: an unusual symptom of transurethral prostatic resection reaction. Anesthesiology 1982;57:332–4.
3. Appelt GL, Benson GS, Corriere JN. Transient blindness: unusual initial symptom of transurethral prostatic resection reaction. Urology 1979;13:402–4.
4. Roesch RP, Stoelting RK, Lingeman JE, et al. Ammonia toxicity resulting from glycine absorption during a transurethral resection of the prostate. Anesthesiology 1983;58:577–9.
5. Hoekstra PT, Kahnoski R, McCannish MA, et al. Transurethral prostatic resection syndrome—a new perspective: encephalopathy with associated hyperammonemia. J Urology 1983; 130:704–7.
6. Charlton AJ. Cardiac arrest during transurethral prostatectomy after absorption of 1.5% glycine. A case report and review of the literature. Anaesthesia 1980,35:804–6.
7. Osborn DE, Rao PN, Greene MJ, Barnard RJ. Fluid absorption during transurethral resection. Br Med J 1980,281:1549–50.
8. Pycock CJ, Kerwin RW. The status of glycine as a supraspinal neurotransmitter. Life Sci 1980;28:2679–86.
9. Markland OH, Garg BP, Brandt IK. Nonketotic hyperglycinemia: electroencephalographic and evoked potential abnormalities. Neurology 1982;32:151–6.
10. Korol S. The effects of glycine on the rabbit retina: averaged ERG and averaged visual evoked responses. Experientia 1973;29(8):984–5.
11. Pritham GH. Anderson's essential of biochemistry. St. Louis, MO: C.V. Mosby Co. 1968;460.
12. Fahey JL. Toxicity and blood ammonia rise resulting from intravenous amino acid administration in man: the protective effect of L-arginine. J Clin Invest 1957;36:1647–55.
13. Fahey JL, Perry RS, McCoy PF. Blood ammonia elevation and toxicity from intravenous L-amino acid administration to dogs: the protective role of L-arginine. Am J Physiol 1958;192(2):311–7.
14. Dustman RE, Beck EC. The effects of maturation and aging on the waveform of visually evoked potentials. Electroencephalogr Clin Neurophysiol 1969;26:2–11.
15. McMartin KE, Ambre JJ, Tephly TR. Methanol poisoning in human subjects. Role for formic acid accumulation in the metabolic acidosis. Am J Med 1980;68:414–8.
16. Martin-Amat G, McMartin KE, Hayreh SS, Hayreh MS, Tephly TR. Methanol poisoning: ocular toxicity produced by formate. Toxicol Appl Pharmacol 1978;45:201–8.
17. Handler P, Kamin H, Harris JS. The metabolism of parenterally administered amino acids. J Biol Chem 1949;179:283–301.
18. Guertzenstein PG, Silver A. Fall in blood pressure produced from discrete regions of the ventral surface of the medulla by glycine and lesions. J Physiol 1974;242:489–503.
19. DeGroat WC. Effects of glycine, GABA and strychnine on sacral parasympathetic preganglionic neurons. Brain Research 1970;18:542–4.
20. Ryall RW, DeGroat WC. The microelectrophoretic administration of noradrenaline, 5-hydroxytryptamine, acetylcholine and glycine to sacral parasympathetic preganglionic neurons. Brain Res 1972;37:345–47.
21. Drinker HR, Shields T, Grayhack JT, et al. Simulated transurethral resection reaction in the dog: early signs and optimal treatment. J Urology 1963;89:595–602.
22. Korol S, Leuenberger PM, Englert U, Babel J. In vivo effects of glycine on retinal ultrastructure and averaged electroretinogram. Brain Res 1975;97:235–51.
23. Domino EF. Effects of preanesthetic and anesthetic drugs on visually evoked responses. Anesthesiology 1967;28:184–97.
24. Uhl RR, Squires KC, Bruce OL, Starr A. Effect of halothane anesthesia on the human cortical visual evoked response. Anesthesiology 1980;53:273–6.

1985;64:1078–80

# Fentanyl Pharmacokinetics and Hemodynamic Effects in Preterm Infants during Ligation of Patent Ductus Arteriosus

C. Collins, FFARCS, G. Koren, MD, P. Crean, FFARCS, J. Klein, MSc, W. L. Roy, FRCP(C), and S. M. MacLeod, MD, PhD, FRCP(C)

COLLINS C, KOREN G, CREAN P, KLEIN J, ROY WL, MACLEOD SM. Fentanyl pharmacokinetics and hemodynamic effects in preterm infants during ligation of patent ductus arteriosus. Anesth Analg 1985;64:1078–80.

*A bolus of 30 μg·kg⁻¹ fentanyl was given to nine preterm infants (gestational age 31.8 ± 4.7 weeks, weight 1100 ± 309 g) for induction of anesthesia for ligation of a patent ductus arteriosus. Thirty minutes after the injection, fentanyl plasma concentrations were between 7.7 and 13.6 ng·ml⁻¹. Elimination half-life was 6–32 hr (mean ± SD, 17.7 ± 9.3). Systolic blood pressure remained stable throughout surgery. There was a gradual increase in heart rate from 159 ± 12 min⁻¹ at the time of skin incision to 173 ± 15 min⁻¹ at the time of skin closure ($P < 0.05$). Fentanyl plasma concentrations remained virtually unchanged between 30 min (10.6 ± 1.9 ng·ml⁻¹) and 120 min (9.6 ± 1.6 ng·ml⁻¹); whereas at the end of surgery most infants moved and breathed spontaneously. This phenomenon can be explained by redistribution of fentanyl from brain into pharmacodynamically inert tissues.*

Key Words: ANALGESICS—fentanyl. ANESTHESIA—pediatric. ANESTHETICS—intravenous.

There is no general agreement on the best anesthetic for preterm infants undergoing surgery for ligation of patent ductus arteriosus (PDA). Robinson and Gregory (1) successfully used high dose fentanyl in this age group (30–50 μg/kg⁻¹). However, plasma concentrations of fentanyl have not been reported, and no relation between plasma concentrations and opioid effects have been studied. The aim of this study was to measure fentanyl plasma concentrations in preterm infants in relation to effects on heart rate (HR), blood pressure (BP), and on wakefulness after surgery.

## Patients and Methods

This study was approved by the Committee for Human Experimentation of the hospital. Nine infants (7 males) with PDA of gestational age 23–38 weeks (mean ± SD, 31.8 ± 4.7 weeks) were studied. At the time of surgery their postconceptional ages were 29–43 weeks and their weights were 710–1625 g (mean, 1100 ± 305 g). Prior to surgery eight of the nine infants required intermittent positive pressure ventilation for cardiorespiratory failure. They all required oxygen with $F_{IO_2}$ between 0.3–0.6 (mean, 0.42). All received a standard restrictive fluid regimen.

No preanesthetic medication was given, and the usual monitoring systems were established, including a precordial stethoscope and rectal and auxiliary temperature probes. Systolic BP was measured using a sphygmomanometer cuff on the right upper arm together with a Doppler ultrasound probe on the right radial artery. Heart rate was measured using a standard II-limb lead electrocardiogram. Transcutaneous oxygen saturation was measured using a Nelcor saturation monitor with an infrared light source probe on the right foot (2). Each infant had an intravenous catheter in situ. The one infant who was not previously mechanically ventilated was intubated and allowed to settle for 5 min before baseline values of BP and HR were recorded.

Neuromuscular blockade was established in seven infants with 0.1 mg·kg⁻¹ pancuronium bromide intravenously; the other two received higher doses (0.2 and 1.0 mg·kg⁻¹) due to dilution errors. Each patient then received a fentanyl bolus of 30 μg·kg⁻¹ intravenously injected within 1 min. The infants were mechanically ventilated with oxygen-enriched air, and the inspired oxygen concentration was adjusted to maintain a transcutaneous oxygen saturation of 80–90%. Blood pressure and HR were monitored and recorded at the following times: baseline; immediately

---

Received from the Departments of Anaesthesia and Division of Clinical Pharmacology, Department of Pediatrics, The Research Institute, The Hospital for Sick Children, Toronto, Ontario. Accepted for publication May 15, 1985.

Address correspondence to Dr. Koren, The Division of Clinical Pharmacology, The Hospital for Sick Children, 555 University Avenue, Toronto, ON M5G 1X8 Canada.

© 1985 by the International Anesthesia Research Society

after fentanyl induction of anesthesia; during skin incision; after ligation of the PDA; during skin closure; and upon return to the neonatal intensive care unit.

### *Fentanyl Plasma Concentrations*

Three 1-ml arterial blood samples were drawn at 30 min, 2 hr, and 6–9 hr after the fentanyl bolus for measurement of fentanyl plasma concentrations. Because of the very low weight of the infants, we considered it unethical to obtain more than three samples for measurement of drug levels. Plasma was separated and stored at −30°C until analyzed. Fentanyl plasma concentrations were analyzed in duplicate using the gas-liquid chromatography method of Gillespie et al. (3). The coefficient of variation within a day was 2.55%. The recovery of fentanyl from plasma varied between 81.5% for 2 ng·ml$^{-1}$ and 85% for 25 ng·ml$^{-1}$. The lowest sensitivity of this test is 0.5 ng·ml$^{-1}$. Fentanyl elimination half-life ($t_{1/2}$) was calculated from the concentration–time data plotted on a semilogarithmic paper by least-squares linear regression analysis.

### *Statistical Analysis*

The differences in the HR and BP at the various stages were compared for each patient by analysis of variance. Results are expressed as mean ± SD.

## Results

### *Fentanyl Plasma Concentrations*

Thirty minutes after bolus injection of 30 μg·kg$^{-1}$ of fentanyl, plasma concentrations of fentanyl were between 7.7 and 13.6 ng·ml$^{-1}$ (mean, 10.6 ± 1.9 ng·ml$^{-1}$). After 2 hr, levels were between 6.6 and 11.5 ng·ml$^{-1}$ (mean, 9.6 ± 1.6 ng·ml$^{-1}$). The levels decreased gradually yielding an elimination half-life ($t_{1/2}$) of 6–32 hr (17.7 ± 9.3 hr). There was no correlation between gestational age, post conceptional age, or weight and elimination $t_{1/2}$) of fentanyl.

### *Cardiovascular Effects of Fentanyl*

After the fentanyl injection, systolic blood pressure remained stable throughout surgery. However, there was a gradual increase in heart rate from 159 ± 12 min$^{-1}$ at the time of skin incision to 173 ± 15 min$^{-1}$ at the time of skin closure ($P < 0.05$) (Fig. 1). These findings agreed with the clinical impression that towards the end of the operation, anesthesia became lighter. The time between arrival in the operating room and return back to the neonatal ICU varied from 85 to 165 min (130 ± 27 min). After the operation, in the neonatal intensive care unit, mean heart rate was 155 ± 10 min$^{-1}$ and mean systolic blood pressure 73 ± 22 mm Hg.

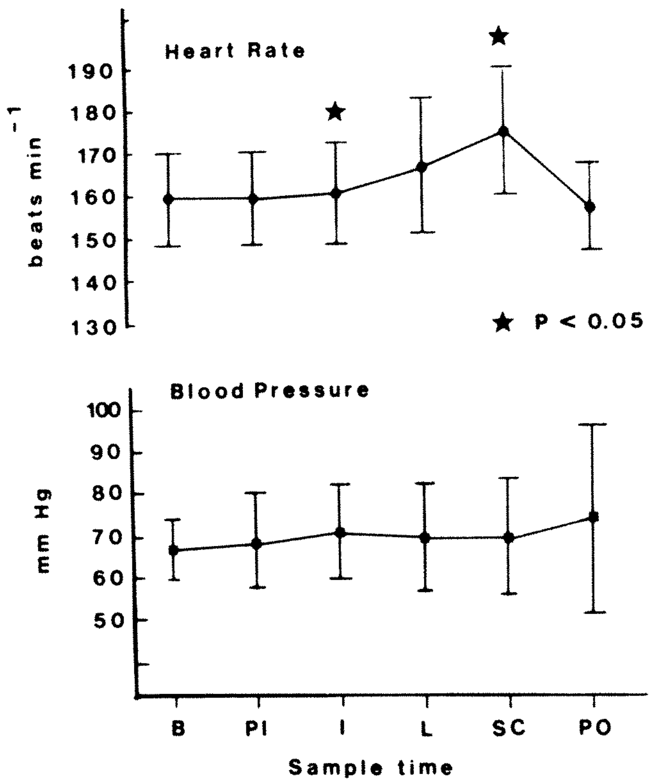


Figure 1. Changes in systolic blood pressure and heart rate after a fentanyl bolus of 30 μg·kg$^{-1}$ in nine preterm infants undergoing ligation of PDA.

Spontaneous movements and respiration were seen in all infants at the time of reversal of neuromuscular blockade with a combination of 50 μg·kg$^{-1}$ of neostigmine and 20 μg·kg$^{-1}$ of atropine intravenously. In seven patients who received 0.1 mg·kg$^{-1}$ of pancuronium, this occurred at the end of the operation, but in the remaining two who had received higher doses of pancuronium (0.2 and 1 mg·kg$^{-1}$), the reversal of neuromuscular blockade was prolonged (3.5 hr and 11 hr, respectively). However, in these two patients the profiles of systolic BP, HR, and for plasma concentrations of fentanyl were identical to the rest of the group.

## Discussion

Our measurements of plasma concentrations of fentanyl indicated that in preterm infants very small changes occur between 30 min and 120 min after the bolus injection of the drug. At the end of surgery most infants moved or breathed spontaneously despite fentanyl plasma concentrations being virtually unchanaged due to the prolonged elimination half-life. This phenomenon has been previously reported by Hug in animal studies and is explained by redistribution of fentanyl from the brain into fat and muscle (9,10) in a fashion similar to thiopental. It is suggested that during redistribution of fentanyl from brain into pharmacodynamically inert compartments, plasma concentration of the drug may not accurately reflect the concentration at the target cells, and therefore may not reflect the anesthetic effect.

Elimination $t_{1/2}$ of fentanyl in our patients was between 6 and 32 hr; however, these calculations were based on three concentration–time points drawn during the first elimination half-life of the drug and therefore should be interpreted cautiously. In older children and adults, elimination $t_{1/2}$ of fentanyl is between 2 and 3 hr (4–7), significantly shorter than in our preterm infants. Elimination rate of many other drugs has been shown to be slower in the preterm infant due to immaturity of hepatic enzymatic processes (8). Lack of correlation between age and elimination $t_{1/2}$ in our patients may be explained by the small size of the study group. Moreover, most of these infants had similar ages (eight were between 29 and 34 weeks postconceptional age). Theoretically, it is possible that the higher doses of pancuronium given to two neonates could have had an effect on the pharmacokinetics of fentanyl in these patients. However, fentanyl levels measured in these infants and the calculated elimination $t_{1/2}$ were not different from the rest of the group. Similarly, the cardiovascular responses in these two patients were identical to the other seven infants.

The hemodynamic profiles of our preterm infants remained relatively constant throughout the surgery, and there was none of the instability previously observed with the use of potent inhalational anesthetics. It did appear that there was some lightening of anesthesia by the time of skin closure with a significant increase in heart rate.

Our studies suggest that a bolus of 30 $\mu g \cdot kg^{-1}$ of fentanyl in preterm infants may not be adequate to cover the increased stimulus of skin closure after closure of a PDA. It may be reasonable to employ a higher dose of fentanyl (e.g., 50 $\mu g \cdot kg^{-1}$) or a continuous infusion of fentanyl. This may cause wakefulness to be delayed, but in practice this is not a problem as current treatment of these infants includes maintaining mechanical ventilation in the immediate postoperative period.

## References

1. Robinson S, Gregory GA. Fentanyl–air–oxygen anesthesia for ligation of patent ductus arteriosus in preterm infants. Anesth Analg 1981;60:331–4.
2. Deckhardt R, Stewart D. Continuous transcutaneous measurement of oxygen saturation. Submitted for publication.
3. Gillespie TJ, Gandolfo AJ, Maiorino RM, Vaughan RW. Gas chromatographic determinations of fentanyl and its analogues in human plasma. J Analyt Toxicol 1981;5:133–7.
4. McClain DA, Hug CC Jr. Intravenous fentanyl kinetics. Clin Pharmacol Ther 1980;28:106–14.
5. Hengtmann JH, Stoeckel H, Schuttler J. Infusion model for fentanyl based on pharmacokinetic analysis. Br J Anaesth 1980;52:1021–5.
6. Koren G, Goresky G, Crean P, Klein J, MacLeod SM. Pediatric fentanyl dosing based on pharmacokinetics during cardiac surgery. Anesth Analg 1984;63:577–82.
7. Johnson KL, Erickson JP, Holley FO, Scott JC. Fentanyl pharmacokinetics in the pediatric population. Anesthesiology 1984;61:A441.
8. Morselli PL, Morselli RF, Bosci L. Clinical Pharmacokinetics in newborns and infants. In: Gibaldi M, Prescott L, eds. Handbook of clinical pharmacokinetics. New York: ADIS Health Science Press, 1983:98–141.
9. Hug CC Jr, Murphy MR. Tissue redistribution of fentanyl and termination of its effects in rats. Anesthesiology 1979;55:309–75.
10. Stanski DR, Hug CC. Alfentanil—a kinetically predictable narcotic analgesic. Anesthesiology 1982;57:35–438.

ANESTH ANALG 1985;64:1081–4

# Heparin, Protamine, and Ionized Calcium In Vitro and In Vivo

Hiroshi Goto, MD, Tamio Kushihashi, MD, Kirk T. Benson, MD, Hitoshi Kato, MD, Deanna K. Fox, MD, and Kasumi Arakawa, MD, PhD

GOTO H, KUSHIHASHI T, BENSON KT, KATO H, FOX DK, ARAKAWA K. Heparin, protamine, and ionized calcium in vitro and in vivo. Anesth Analg 1985;64:1081–4.

*The possibility that hypotension associated with protamine or heparin might be related to changes in levels of serum ionized calcium values was determined by in vitro and in vivo studies in dogs. In vitro protamine did not decrease serum calcium levels, but heparin did in a dose-dependent fashion. The reduction ranged from 7% with 10 units/ml of heparin to 20% with 100 units/ml of heparin. Ionized calcium concentrations initially decreased by heparin were restored toward control levels by our increasing the dose of protamine, indicating that the electrostatic attraction between protamine and heparin molecules is stronger than that between heparin and ionized calcium. Despite significant reductions in blood pressure and heart rate, clinical doses of protamine did not decrease ionized calcium in vivo. Although the results of the in vitro study suggested that heparin-induced hypocalcemia might occur in vivo, in vivo heparin caused neither a decrease in ionized calcium nor hypotension. The reduction of ionized calcium by heparin might have been rapidly compensated for in vivo. The results indicate that hypotension due to protamine or heparin is unlikely to be related to changes in serum ionized calcium levels.*

Key Words: BLOOD, COAGULATION—heparin, protamine. IONS—calcium.

Despite the long-established clinical use of protamine sulfate, controversy still exists concerning the mechanisms of its hypotensive effect. It has been postulated that reduction of serum concentrations of ionized calcium is one of the responsible mechanisms (1). Heparin is also known to cause hypotension, although it is uncommon (2). Unlike protamine, heparin is a negatively charged mucopolysaccharide (3). Thus it might be heparin that decreases positively charged serum ionized calcium. We were interested in how protamine and heparin would interact with ionized calcium in vitro and in vivo.

## Methods

### In Vitro Study, Part 1

Venous blood was obtained from six mongrel dogs. The serum was separated by centrifugation (15 min × 2500 rpm) and was pooled. Distilled deionized water (DDW) was prepared by running distilled water through a Millipore system (Millipore Corporation) until the specific resistance became greater than 18 mΩ/cm. Serum, 0.9 ml, was introduced into polypropylene test tubes (Fisher Scientific), and a total volume of 0.1 ml of DDW with various amounts of either protamine (Upjohn Company) or heparin (Upjohn Company) was added. Doses of protamine and heparin ranged from 0 to 1000 μg and from 0 to 100 units, respectively.

Each 1-ml sample was incubated in a 37°C water bath for a period of 30 min. Ionized calcium was measured with an ion-selective electrode (AM 722, Applied Medical Technology) five times for each sample. The electrode was calibrated with the standard solutions of high ($Ca^{2+}$, 2.10 mM) and low ($Ca^{2+}$, 1.05 mM) calibration solutions.

### In Vitro Study, Part 2

Heparin, 10 units or 20 units in DDW (total volume 0.1 ml), was added to 0.8 ml of serum. Then protamine, in doses increasing from 0 to 1000 μg in DDW (total volume 0.1 ml), was added, making a total volume of 1.0 ml. Ionized calcium was measured as in the part 1 study. Mean values of percentage changes from each control ionized calcium level were plotted with respect to protamine and heparin concentrations.

---

Presented in part at the Annual Meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, October 1984.

Received from the Department of Anesthesiology, University of Kansas Medical Center, Kansas City, Kansas. Accepted for publication June 4, 1985.

Address correspondence to Dr. Goto, Department of Anesthesiology, University of Kansas Medical Center, Kansas City, KS 66103.

© 1985 by the International Anesthesia Research Society

### *In Vivo Study*

Twelve mongrel dogs weighing 18.5–30.8 kg were anesthetized with 30 mg/kg pentobarbital intravenously, intubated, paralyzed with 0.1 mg/kg pancuronium bromide, and mechanically ventilated. Anesthesia was maintained with 0.5–1.0% enflurane in oxygen. Ventilation was adjusted to achieve normal ranges of arterial pH values. A femoral artery was cannulated, and blood pressure was continuously recorded with a Hewlett–Packard 7758 eight-channel recording system, along with a lead II electrocardiogram.

After a steady state was achieved, six dogs received 4 mg/kg protamine over 30 sec, and another six dogs received 300 units/kg heparin over 30 sec. Arterial blood samples were obtained for measurement of gas tensions, pH, and ionized calcium levels 5 min before and 1, 5, and 10 min after administration of each drug. Student's *t*-test was used for statistical analysis, with *P* values less than 0.05 considered significant.

## Results

### *In Vitro Study*

Protamine, even in high concentrations of 1000 µg/ml, did not decrease ionized calcium. On the other hand, heparin decreased ionized calcium in a dose-dependent fashion (Fig. 1). Ionized calcium was decreased approximately 7% by heparin, 10 units/ml, and 20% by heparin, 100 units/ml. Ionized calcium concentration, which initially had been decreased by heparin, 10 units/ml and 20 units/ml, was restored toward the control level by an increase in the doses of protamine concentrations (Fig. 2). The ionized calcium value was completely restored by protamine, 400 µg/ml, when 10 units of heparin were present and by protamine, 900 µg/ml, when 20 units of heparin were present.

### *In Vivo Study*

Table 1 shows the changes in ionized calcium ($Ca^{2+}$), mean arterial pressure (MAP), heart rate (HR), $Pa_{O_2}$, $Pa_{CO_2}$, and pHa after administration of 4 mg/kg of protamine. Significant changes were observed only in the mean blood pressure and heart rate after 1 min. After administration of 300 units/kg of heparin, none of the parameters measured had changed significantly (Table 2).

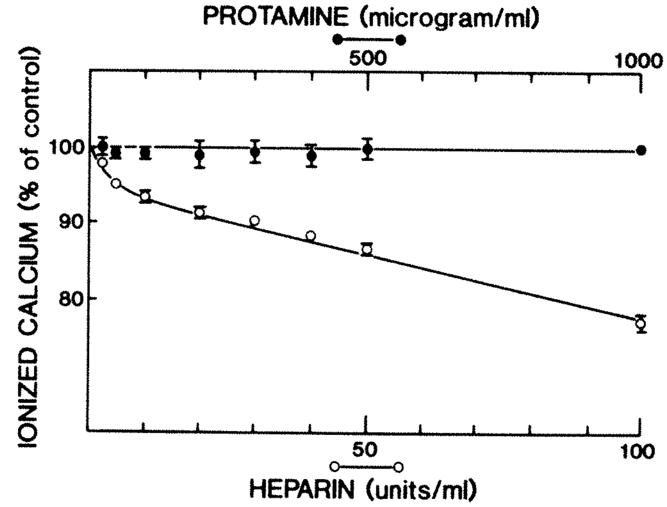


Figure 1. The percent changes of ionized calcium (mean ± SEM) plotted with respect to protamine and heparin concentrations.

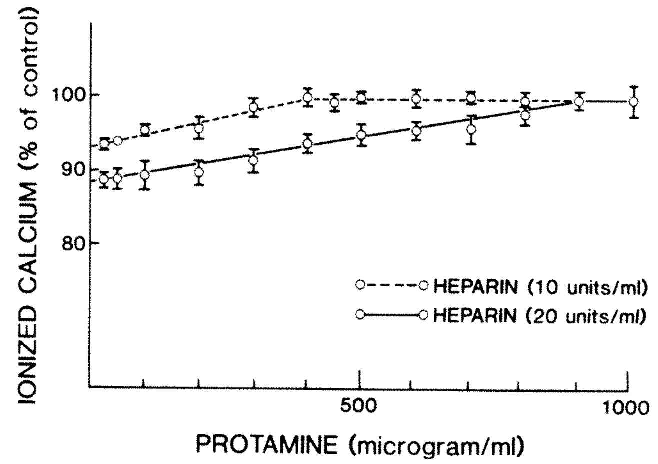


Figure 2. The percent changes of ionized calcium (mean ± SEM) by fixed heparin concentration with increases in protamine concentration.

## Discussion

Protamine is a strongly cationic basic protein with a molecular weight of 4626 ± 109 (3,4). It is abundant in cell nuclei of fish sperm. Because it is a heterogeneous macromolecule, protamine could have anionic sites on its structure (5). However, protamine did not decrease the positively charged serum ionized calcium level, indicating that the anionic sites on protamine molecules are negligible, if there are any. Jones et al. stated (1) that protamine is a large, negatively charged molecule that may be capable of binding ionized calcium ($Ca^{2+}$). The results of our in vitro study indicate that this is unlikely.

Heparin is a highly sulfated negatively charged mucopolysaccharide; its molecular weight ranges from 6000 to 20,000 depending on the source and the method of determination (3). Heparin dose-related decrease in calcium ion activity has been reported previously using human serum (5). We also could demonstrate a very similar dose-dependent reduction of canine

Table 1. Effect of 4 mg/kg Protamine Administration

| | $Ca^{2+}$ (mmol/L) | MAP (mm Hg) | Heart rate | $Pa_{O_2}$ (mm Hg) | $Pa_{CO_2}$ (mm Hg) | pHa |
|---|---|---|---|---|---|---|
| Control | 1.25 ± 0.06 | 100.0 ± 4.5 | 122.0 ± 3.3 | 505.8 ± 22.6 | 36.8 ± 4.0 | 7.34 ± 0.02 |
| 1 min | 1.24 ± 0.03 | 51.0 ± 11.6[a] | 113.6 ± 3.1[a] | 505.2 ± 24.1 | 32.0 ± 3.6 | 7.36 ± 0.02 |
| 5 min | 1.22 ± 0.04 | 89.0 ± 18.9 | 117.2 ± 4.5 | 475.2 ± 32.1 | 35.6 ± 3.3 | 7.32 ± 0.03 |
| 10 min | 1.22 ± 0.06 | 116.3 ± 11.1 | 119.6 ± 4.8 | 485.2 ± 26.0 | 37.9 ± 4.1 | 7.29 ± 0.05 |

[a] $P < 0.05$.
$n = 6$ (mean ± SE).

Table 2. Effect of 300 Units/kg Heparin Administration

| | $Ca^{2+}$ (mmol/L) | MAP (mm Hg) | Heart rate | $Pa_{O_2}$ (mm Hg) | $Pa_{CO_2}$ (mm Hg) | pHa |
|---|---|---|---|---|---|---|
| Control | 1.14 ± 0.10 | 99.0 ± 5.0 | 113.2 ± 5.2 | 508.2 ± 17.0 | 26.1 ± 1.3 | 7.42 ± 0.03 |
| 1 min | 1.18 ± 0.08 | 102.6 ± 7.1 | 113.7 ± 5.2 | 508.3 ± 19.4 | 27.7 ± 3.3 | 7.42 ± 0.03 |
| 5 min | 1.17 ± 0.08 | 103.7 ± 7.2 | 116.4 ± 4.4 | 497.8 ± 9.7 | 26.4 ± 2.9 | 7.43 ± 0.03 |
| 10 min | 1.16 ± 0.07 | 111.3 ± 8.3 | 113.6 ± 6.5 | 512.7 ± 8.9 | 27.8 ± 3.8 | 7.44 ± 0.03 |

$n = 6$ (mean ± SE).

serum ionized calcium concentration, which is thought to be due to the electrostatic attraction between negatively charged heparin molecules and positively charged calcium ions. Heparin, 10 units/ml of serum, decreased ionized calcium by about 7%. This dose is approximately equivalent to the clinical heparin dose of 350 units/kg for extracorporeal bypass, provided by the blood volume of patients—65 ml/kg and the hematocrit 45 (350 units/65 × 0.55).

Initially decreased ionized calcium levels were restored toward the control value by the addition of increasing doses of protamine. Therefore, it is thought that protamine molecules combine with heparin at the sites where ionized calcium has been bound. This indicates that the electrostatic attraction between protamine and heparin is stronger than that between heparin and ionized calcium. Recently, it was confirmed that the heparin–protamine interaction is due to simple physical charge-to-charge attraction (6).

According to the protamine package insert, 1 mg of protamine neutralizes approximately 100 units of heparin. Thus 100 μg and 200 μg of protamine are neutralizing doses for 10 units and 20 units of heparin, respectively. These were used in part 2 of the in vitro study. When protamine doses reached 400 μg, ionized calcium levels reduced by 10 units of heparin were returned completely to the control values. Ionized calcium levels reduced by 20 units of heparin were restored by 900 μg of protamine. This indicates that protamine molecules can bind to heparin and to already formed heparin–protamine complex, at least until up to 4–4.5 times of the neutralizing protamine dose is added.

Possible mechanisms of protamine-induced hypotension have been studied both in humans and dogs. These include myocardial depression (7), decrease in systemic vascular resistance (8), increase in pulmonary artery pressure (9), histamine release (10), immune-mediated anaphylaxis (11), nonimmunologic anaphylactoid reaction (12), and reduction of serum ionized calcium level (1). In contrast to humans, dogs appear to be hemodynamically vulnerable to intravascular administration of protamine (13). The reason for this has not been elucidated; the main purpose of these protamine studies using dogs has been to investigate the mechanism of protamine-induced hypotension rather than to investigate species differences. Likewise, the purpose of our study is to investigate the interaction of serum ionized calcium and protamine in vitro and in vivo using dogs to find out whether or not serum ionized calcium concentration plays a role in protamine-induced hypotension. It was not our intent to study the hemodynamic sensitivity of dogs to the reduction of serum ionized calcium levels that might occur after protamine administration.

Whether or not protamine is capable of decreasing ionized calcium in vivo is controversial. Jones et al. (1) demonstrated in the dog that 3 mg/kg protamine administered 30 min after 300 units/kg of heparin caused a significant reduction of ionized calcium at 1, 2, 3, and 4 min. Conahan et al. (14) could not demonstrate the decrease in both ionized and total calcium in humans by 3 mg/kg of protamine given in order to neutralize heparin. In our in vivo study with dogs, 4 mg/kg of protamine alone did not cause hypocalcemia, as had been expected by the results of our in vitro study. Therefore, more studies need to be carried out in order to elucidate the in vivo interaction of protamine and serum ionized calcium. Johnston et al. (15) suggested that protamine alone could produce hypocalcemia by direct inhibition of bone absorption. However, this seems to be a slow process and must not have occurred immediately after protamine administration.

Although heparin-induced hypotension is rare, several possible mechanisms have been postulated. These include systemic vasodilation (16), histamine-like activity in the heparin preparation (17), and myocardial depression (18). Seltzer and Gerson (2) observed hypotension after 300 units/kg of heparin were administered to a human subject and concluded that heparin-induced hypotension was due to the reduction of systemic vascular resistance rather than to myocardial depression. Csaba and Horvath (18) observed that heparin reduced the contractility of the isolated frog heart and that this was antagonized by calcium chloride but not epinephrine. Their observation and our in vitro study suggest that heparin might decrease ionized calcium in vivo. However, it caused neither hypotension nor hypocalcemia in our dog preparation. Reduced ionized calcium may be restored immediately by the compensatory mechanism in which plasma proteins and musculoskeletal tissues release ionized calcium.

In summary, hypotension induced either by protamine or by heparin is unlikely to be related to changes in concentrations of ionized calcium in serum.

## References

1. Jones RM, Hill AB, Nahrwold ML, Tait AR. Effect of protamine on plasma ionized calcium in the dog. Can Anaesth Soc J 1982;29:65–7.
2. Seltzer JL, Gerson JI. Decrease in arterial pressure following heparin injection prior to cardiopulmonary bypass. Acta Anaesthesiol Scand 1979;23:575–8.
3. O'Reilly. Anticoagulant, antithrombotic, and thrombolytic drugs. In: Goodman LS, Gilman A, eds. The pharmacological basis of therapeutics. New York: Macmillan, 1980:1347–66.
4. Cobel-Geard RJ, Hassouna HI. Interaction of protamine sulfate with thrombin. Am J Hematol 1983;14:227–33.
5. Ladenson JH, Bowers GN. Free calcium in serum. I. Determination with the ion-specific electrode, and factors affecting the results. Clin Chem 1973;19:565–74.
6. Poon MC, Hurst RE, Rives MS. Platelet factor four and protamine sulfate neutralization of heparin fractionated according to anionic charge density. Thromb Haemost 1982;47:162–5.
7. Fadali MA, Ledbetter M, Papacostas CA, Duke LJ, Lemole GM. Mechanism responsible for the cardiovascular depressant effect of protamine sulfate. Ann Surg 1974;180:232–5.
8. Goldman BS, Joison J, Austen WG. Cardiovascular effects of protamine sulfate. Ann Thorac Surg 1969;7:459–71.
9. Lowenstein E, Johnston WE, Lappas DG, et al. Catastrophic pulmonary vasoconstriction associated with protamine reversal of heparin. Anesthesiology 1983;59:470–3.
10. Frater RWM, Oka Y, Hong Y, Tsubo T, Loubser PG. Protamine-induced circulatory changes. J Thorac Cardiovasc Surg 1984;87:687–92.
11. Knape JTA, Schuller JL, DeHaan P, DeJong AP, Bovill JG. An anaphylactic reaction to protamine in a patient allergic to fish. Anesthesiology 1981;55:324–5.
12. Campbell FW, Goldstein MF, Atkins PC. Management of the patient with protamine hypersensitivity for cardiac surgery. Anesthesiology 1984;61:761–4.
13. Horrow JC. Protamine: a review of its toxicity. Anesth Analg 1985;64:348–61.
14. Conahan TJ III, Andrews RW, MacVaugh H III. Cardiovascular effects of protamine sulfate in man. Anesth Analg 1981;60:33–6.
15. Johnston CC, Grinnan EL, Wilson HC, Boderl GB. Protamine-induced hypocalcemia. Endocrinology 1970;87:1211–7.
16. Gabor M, Antal A, Dirner Z. Effect of anticoagulants on the capillary resistance of internal organs of rats. J Pharm Pharmacol 1967;19:488.
17. Green JP, Day M, Roberts M. On the smooth-muscle stimulating activity of preparations of heparin. J Pharmacol Exp Ther 1961;132:58–64.
18. Csaba G, Horvath C. The effect of heparin and its components on frog hearts. Biochem Pharmacol 1963;12:1075–80.

ANESTH ANALG 1985;64:1085–8

# The Effect of Epidural Somatostatin on Postoperative Pain

Joachim Chrubasik, MD, Jacques Meynadier, MD, Phillippe Scherpereel, MD, and Erich Wünsch, PhD

CHRUBASIK J, MEYNADIER J, SCHERPEREEL P, WÜNSCH E. The effect of epidural somatostatin on postoperative pain. Anesth Analg 1985;64:1085–8.

*The epidural injection of a bolus of 250 μg somatostatin followed by continuous epidural infusion provided complete postoperative relief of pain in eight patients who had undergone abdominal surgery; no other analgesics were required. In two patients, intravenous and intramuscular naloxone had no effect on the analgesia provided by epidural somatostatin. In two patients, epidural somatostatin also produced adequate intraoperative analgesia. Epidural somatostatin was associated with no side effects.*

Key Words: PAIN—postoperative. ANESTHETIC TECHNIQUES, EPIDURAL—somatostatin. HORMONES—somatostatin.

Because of its reliable analgesic effect, morphine is the most widely used opiate for management of acute and chronic pain by epidural injection (1–4). In a preliminary report, epidural somatostatin has also been described as being effective in the treatment of pain (5). Indeed, epidural somatostatin seems to alleviate pain as effectively as epidural morphine. In the present paper, we describe eight patients given epidural somatostatin to provide analgesia in the early postoperative period.

## Methods

Eight patients (ASA class III) undergoing abdominal surgery were investigated after their informed consent and the approval of the hospital review board had been obtained. All patients were given 0.25 mg atropine and 50 mg chlorazepam for premedication. The clinical details of the patients are summarized in Table 1. Immediately before the operation, an epidural catheter was placed in the epidural space at a level between the sixth thoracic and the first lumbar vertebrae, depending on the site of surgery. A test dose of 3 ml mepivacaine was administered to verify the epidural positioning of the catheter. Six of the eight patients had general anesthesia with barbiturates, nitrous oxide–oxygen–isoflurane, pancuronium, and fentanyl-balanced anesthesia. Two patients received a bolus epidural injection of 250 μg somatostatin prior to an infusion of 250 μg/hr (a total of 1.0 and 2.4 mg somatostatin) for operative anesthesia instead of fentanyl and isoflurane (6). One of the two required a total of 35 mg diazepam for sedation during a 4.5-hr operation.

Pain scores were assessed postoperatively by a modified pain analogue scale (no pain, 0; worst pain, 10). So that pain might be treated on an individual basis, patients were asked about their subjective pain frequently and at the preset intervals of the project protocol (at the beginning of the treatment, 1 and 2 hr after commencement of the treatment, at 8 PM on the operation day, and subsequently every 12 hr until 8 PM on the second postoperative day). The patients also were told that they should ring for the nurse, should they have any discomfort or pain.

As soon as the patients complained of pain after the operation, 250 μg somatostatin in 1 ml isotonic saline solution was administered by syringe through the epidural catheter already in place. After the bolus epidural injection, 125 μg somatostatin contained in 0.6 ml of saline was infused each hour by means of a small, externally worn device (Pharmacia, Act-A-Pump 1000). The dosages chosen were based on experience with treatment of chronic pain (5). During the first hour of the infusion, no supplementary analgesics were administered. If after 60 min or at any time throughout the rest of the first two postoperative days the pain score exceeded 3, further bolus epidural

---

Received from University Hospital, Düsseldorf, Federal Republic of Germany; the Departments of Anesthesia, Centre Oscar Lambret and the University of Lille, Lille, France; and the Max Planck Institute of Biochemistry, Munich, Federal Republic of Germany. Accepted for publication June 3, 1985.

Address correspondence to Dr. Chrubasik, Department of Anesthesiology, University Hospital, Moorenstrasse 5, 4 Düsseldorf, Federal Republic of Germany.

© 1985 by the International Anesthesia Research Society

Table 1. Operations and Clinical Data of the Patients

| | Patients receiving somatostatin | Patients in control group |
|---|---|---|
| Type of operation | | |
| Hysterectomy[a] | 4 | 4 |
| Adrenalectomy[a] | 1 | 1 |
| Lymphadenectomy[a] | 1 | 1 |
| Palliative abdominal operation[a] | 2 | 2 |
| Clinical data | | |
| Age (yr) | 56 ± 11[b] | 56 ± 11[b] |
| Weight (kg) | 67 ± 14[b] | 75 ± 12[b] |
| Size (cm) | 163 ± 9[b] | 166 ± 7[b] |
| Male: female | 1:7 | 1:7 |
| Length of operation (min) | 154 ± 83[b] | 137 ± 28[b] |

[a] Number of patients.
[b] Mean ± SD.

injections of 250 μg somatostatin were administered by syringe in order to titrate individual somatostatin requirement. If the pain score remained at zero for at least 3 hr during a 12-hr period, the basal dose rate was reduced at a predetermined rate of 0.2 ml/hr every 12 hr, starting at 8 PM on the day of operation.

Two arbitrarily selected patients received, with their consent, 0.4 mg naloxone intravenously and 0.8 mg intramuscularly at 8 PM on the day of operation. This was done to evaluate whether a classic narcotic antagonist might affect the analgesia provided by epidural somatostatin.

In addition to regular supervision, blood pressure, pulse, and respiratory rates were measured twice daily until the second postoperative day. Blood samples were taken prior to the operation, at 8 AM on the operation day, and the first, second, and third postoperative days to measure white blood cell count, platelet count, liver function and concentrations of hemoglobin, blood glucose, electrolytes, creatinine, urea, protein, lipids, and amylase. Urine output was also measured.

A control group of eight patients (Table 1) received bolus intramuscular injections of buprenorphine, a potent analgesic and partial opiate antagonist (7), for alleviation of postoperative pain. The "matched pair" selection criteria included a similar ASA status and operation, approximately the same age, and a similar weight category (normal, overweight, underweight).

## Results

Within 15 min after the bolus epidural injection of somatostatin, analgesia was attained in all patients. During the course of the somatostatin epidural infusion, however, three patients complained of increasing pain, which necessitated an extra bolus epidural injection of somatostatin 60 min after the first injection. The pain score in all patients after 60 min was 3.8 ± 1.1 (±SEM), and after 2 hr, 1.8 ± 0.5 (±SEM). Three additional patients required up to seven epidural injections of 250 μg somatostatin in addition to the constant epidural infusion of somatostatin. Two of those three required sedation during the night in order to sleep, for which a total of 12.5 and 20 mg diazepam was given. Individual patterns of the epidural infusion rates of somatostatin in all patients are presented in Figure 1. None of the eight patients needed any other analgesic. Moreover, administration of naloxone (0.4 mg intravenously and 0.8 mg intramuscularly) in two patients did not affect the analgesia maintained by epidural somatostatin.

Total dose of postoperative somatostatin given up to 8 PM on the second postoperative day averaged 6.2 ± 0.8 mg (±SEM) (range 2.4–8.8 mg). The patients who received naloxone had 2.6 and 4.8 mg somatostatin, respectively. The total dose of buprenorphine given postoperatively in the control patients averaged 0.5 ± 0.1 mg (±SEM) (range 0.3 –1.2 mg).

When epidural somatostatin was given as the sole intraoperative analgesic blood pressure, heart rate and perspiration showed no change that indicated inadequate analgesia in the course of the operation. Likewise the absence of gross effects on respiration or cardiovascular function agrees with adequate analgesia in the early postoperative period. Blood chemistries, with the exception of blood glucose, were normal, as was urinary output. Although epidural somatostatin can affect blood glucose levels, the increase in blood glucose levels observed postoperatively was probably related to postoperative glucose intravenous infusion. None of the patients complained of side effects, and there were no complications.

## Discussion

Although an economical method of producing somatostatin on a large scale has been developed recently (8), clinical use of the peptide has essentially remained limited to occasional treatment of gastrointestinal fistulas (9,10) and hemorrhage from peptic ulcers (11). With bleeding ulcers, high doses (up to 6 mg somatostatin per 24 hr intravenously over more than 2 weeks) caused no discomfort or clinically significant biochemical side effects. Because the blood–brain barrier restricts peptide penetration (12), no central side effects were observed in patients under treatment with intravenous somatostatin.

Somatostatin has been demonstrated to exist in several regions of the central nervous system (13,14),

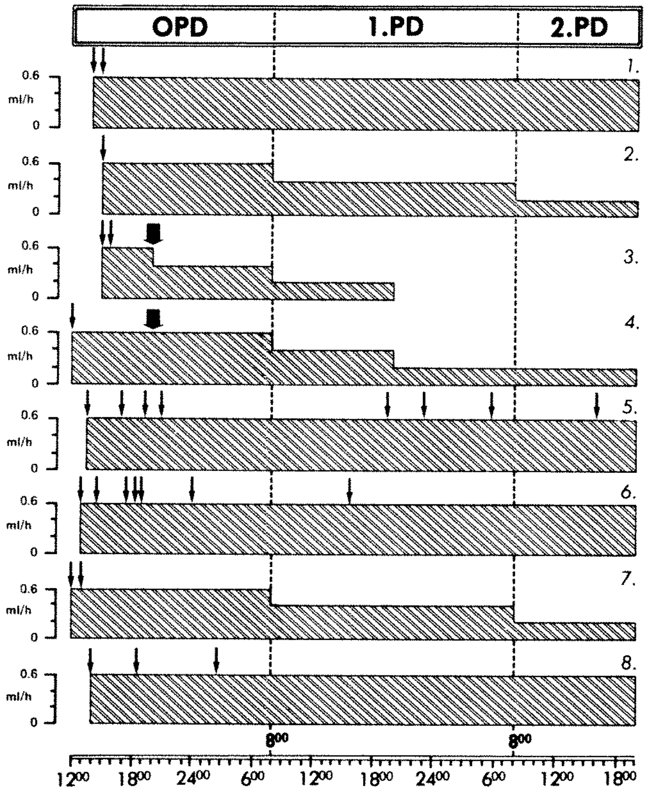


Figure 1. Patterns of amounts of epidural somatostatin needed to relieve pain in eight patients on the day of operation (OPD) and on the first two postoperative days (1.PD and 2.PD). Symbols: thin arrows, bolus epidural injection of 250 $\mu$g somatostatin (in addition to continuous epidural infusion); thick arrow, time of administration of naloxone (0.4 mg intravenous and 0.8 mg intramuscular) in two patients.

indicating that this tetradecapeptide might be involved in the function of the central nervous system. Investigations in rats provided the first experimental evidence that somatostatin might have an analgesic effect when injected into cerebrospinal fluid (CSF) (5,15). In humans, intrathecal and intraventricular administration of somatostatin has proved to be as effective as morphine in the treatment of chronic pain (5). Epidural administration of somatostatin, however, at least theoretically, seemed less likely to produce analgesia because, unlike morphine (16), only small amounts of somatostatin penetrate the dura mater (5). The results of our study show, however, that epidural somatostatin is effective in relieving acute pain. The patients in the control group, matched in ASA category, age, weight, and type of operation, required considerable analgesic treatment. Patients given epidural somatostatin required no other postoperative analgesic. Thus very low concentrations of somatostatin in the CSF are capable of inducing potent analgesia, as has been confirmed in successful intrathecal treatment of cancer pain for up to 60 days by intrathecal infusion of somatostatin, at rates of up to 50 $\mu$g per hour (17).

We found that maintenance of analgesia in the early postoperative period with epidural somatostatin requires continuous epidural infusion. The somatostatin requirement varied greatly from patient to patient as did the amount of morphine needed when given by continuous-plus-on-demand epidural infusion after abdominal operations (18). Epidural somatostatin, however, does not appear to produce sedation, and patients remained alert and cooperative postoperatively. To achieve a higher degree of sedation both during and after the operation, supplementary administration of diazepam proved necessary in some of the patients.

Although opiate receptors are involved in the mediation of analgesia by somatostatin in rats (15,19), administration of naloxone to two of our postoperative patients did not reverse the analgesic effect of somatostatin when administered in doses high enough to influence the analgesic effect of morphine (20). Recently, somatostatin receptors were shown to exist throughout the central nervous system (21), so it seems likely that somatostatin acts on its own receptor sites, which need not necessarily be opiate receptor sites.

In summary, continuous epidural administration of somatostatin produced adequate analgesia in the early postoperative period. Serious side effects did not occur.

The authors thank Professor Dr. A. Demaille for his support of this project and G. Harrant, CuraMED GmbH, Freiburg, and Dr. W. Kolbeck, Diamalt AG, Munich, West Germany, for providing the somatostatin.

## References

1. Behar M, Magora F, Olshwang D, Davidson JT. Epidural morphine in treatment of pain. Lancet 1979;i:527–9.
2. Chrubasik J. Epidural, on-demand, low-dose morphine infusion for postoperative pain. Lancet 1984;i:107–8.
3. Chrubasik J. Low-dose epidural morphine by infusion pump. Lancet 1984;i:738–9.
4. Coombs DW, Saunders L, Gaylor M, Pageau MG. Epidural narcotic infusion reservoir: implantation technique and efficacy. Anesthesiology 1982;56:469–73.
5. Chrubasik J, Meynadier J, Blond S, Scherpereel P, Ackerman E, Weinstock M, Bonath K, Cramer H, Wünsch E. Somatostatin: a potent analgesic substance. Lancet 1984;ii:1208–9.
6. Chrubasik J, Meynadier J, Scherpereel P, Magora F, Davidson J, Wünsch E. Erste Untersuchungen zur intraoperativen Anwendung spinal applizierten Somatostatins. Anaesth Intensivther Notfallmed 1985;20:139–42.
7. Mok MS, Lippmann M, Steen SN. Multidose/observational,

comparative clinical analgetic evaluation of buprenorphine. J Clin Pharmacol 1981;21:323–9.

8. Moroder L, Gemeiner M, Goehring W, Jaeger E, Thamm P, Wünsch E. New synthesis of somatostatin according to the s-tert-butylthiocysteine procedure. Bio Polymers 1981;20:17–37.
9. diConstanzo J, Cano N, Martin M. Somatostatin in persistent gastrointestinal fistula treated by total parenteral nutrition. Lancet 1982;ii:338–9.
10. Hild P, Stoyanov M, Dobroschke J, Aigner K. La somatostatine dans le traitement médical des fistules du pancreas et de l'intestine grele. Sem Hop Paris 1982;58:2195–8.
11. Kayasseh L, Gyr K, Keller U, Stalder GA, Wall M. Somatostatin and cimetidine in peptic ulcer haemorrhage. Lancet 1980;i:844–5.
12. Cornford EM, Braun LD, Crane PD, Oldendorf WH. Blood–brain barrier restriction of peptides and the low uptake of enkephalins. Endocrinology 1978;103:1297–303.
13. Luft R, Efendic S, Hökfelt T. Somatostatin—both hormone and neurotransmitter? Diabetologia 1978;14:1–13.
14. Patel YC, Rao K, Reichlin S. Somatostatin in human cerebrospinal fluid. N Engl J Med 1977;296:529–33.
15. Rezek M, Havlizek V, Leybin L, LaBella FS, Friesen H. Opiate-like naloxone-reversible actions of somatostatin given intracerebrally. Can J Physiol Pharmacol 1978;56:227–31.
16. Nordberg G, Hedner T, Mellstrand T, Borg L. Pharmacokinetics of epidural morphine in man. Eur J Clin Pharmacol 1984;26:233–7.
17. Meynadier J, Chrubasik J, Dubar M, Wünsch E. Intrathecal somatostatin in two terminally ill patients. Pain (in press).
18. Chrubasik J, Wiemers K. Continuous-plus-on-demand epidural infusion of morphine for postoperative pain relief by means of a small, externally worn infusion device. Anesthesiology 1985;62:263–7.
19. Terenius L. Somatostatin and ACTH are peptides with partial antagonist-like selectivity for opiate receptors. Eur J Pharmacol 1976;38:211–3.
20. Gattiker R, Dimai W, Berlin J, Hossli G. Aufhebung der Atemdämpfung durch Naloxone nach hochdosierter Fentanyl-Anaesthesie in der Gefässchirurgie. Anaesthesist 1978;27:267–71.
21. Srikant CB, Patel YC. Somatostatin receptors: identification and characterization in rat brain membranes. Proc Nat Acad Sci 1981;78:3930–4.

ANESTH ANALG 1985;64:1089–96

# Bupivacaine-Induced Cardiotoxicity in Hypoxic and Acidotic Sheep

Mark A. Rosen, MD, Jarman W. Thigpen, MD, Sol M. Shnider, MD, Stanley E. Foutz, MD, Gershon Levinson, MD, and Minako Koike, MD

ROSEN MA, THIGPEN JW, SHNIDER SM, FOUTZ SE, LEVINSON G, KOIKE M. Bupivacaine-induced cardiotoxicity in hypoxic and acidotic sheep. Anesth Analg 1985;64:1089–96.

*Awake, unanesthetized, and paralyzed sheep made hypoxic and acidotic were given equivalent low and high intravenous doses of lidocaine and bupivacaine over 10 sec. Within 30 sec of injections, all animals had electroencephalographic evidence of convulsions. After administration of low-dose lidocaine, arrhythmias associated with significant hemodynamic changes did not occur; after administration of high-dose lidocaine, half of the animals became hypotensive but had no arrhythmias other than sinus tachycardia. However, after administration of low-dose bupivacaine, all sheep had evidence of serious electrocardiographic changes or arrhythmias, and one animal died. After administration of high-dose bupivacaine, serious electrocardiographic changes occurred in all animals, and despite resuscitative efforts, all died. The most common abnormality after bupivacaine administration was a wide-QRS-complex bradycardia, occurring in most animals regardless of dose. Two-thirds of the animals given high-dose bupivacaine had electromechanical dissociation and subsequent refractory asystole. Although the mechanism of action is not known, bupivacaine appears to be more cardiotoxic than lidocaine. This toxicity is enhanced in animals by the presence of hypercarbia, acidosis, and hypoxia.*

Key Words: ANESTHETICS, LOCAL—bupivacaine, lidocaine. HEART—arrhythmia. TOXICITY—local anesthetic.

In a previous study of the effects of bupivacaine and lidocaine in unpremedicated conscious sheep, rapid intravenous injection of convulsant (or higher) doses of bupivacaine produced severe cardiac arrhythmias (1). Despite the use of relatively high-dose bupivacaine (4.2 mg/kg), most of these animals survived after only minimal therapy. These results do not explain the fatal cardiac arrests in humans after accidental intravenous injection of bupivacaine (2,3). Humans may quickly become severely hypoxic and acidotic after seizure (4), whereas the conscious sheep hyperventilated and became neither hypoxic nor acidotic. Thus the present study is designed to simulate more closely the accidental intravenous injection of local anesthetic that rapidly produces hypoxia and acidosis in humans.

## Methods

After approval of our Committee on Animal Research, ewes 2–3 yr of age weighing 32–59 kg had preparatory surgery while anesthetized with halothane in oxygen. Polyvinyl catheters were inserted into a femoral artery for continuous recording of blood pressure, into a femoral vein for drug injection, and into a carotid artery for obtaining blood samples. A flow-directed pulmonary artery catheter with atrial and ventricular pacing electrodes was inserted through a neck incision via the internal jugular vein to record intracardiac electrocardiogram (ECG). A tracheostomy was performed, and a #9 cuffed Portex tracheostomy tube was left in place to facilitate adequate ventilation. Two metallic screws were inserted into the cranium approximately 1 cm on each side of the midline in the parietal bone for continuous monitoring of the electroencephalogram (EEG). Animals were allowed to recover for at least 24 hr.

On the study day, ewes were paralyzed with succinylcholine, 2 mg/kg, and their lungs ventilated with room air to maintain a normal $Pa_{CO_2}$. Surface and intracardiac ECG, EEG, and arterial pressures were recorded continuously on a Grass polygraph. After a 30-min control period, acute respiratory acidosis was induced by ventilation with a mixture of air and 12% $CO_2$; analyses of arterial blood gases were performed 3, 5, and 8 min later. Eight minutes after the induction of hypercapnia, the following blood gas values (mean ± SEM) were obtained: pHa, 7.15 ± 0.07; $Pa_{O_2}$, 50 ± 15 mm Hg; and $Pa_{CO_2}$, 85 ± 10 mm Hg. During the

---

This work was supported in part by the Anesthesia Research Foundation. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, Atlanta, Georgia, October 1983.

Received from the Department of Anesthesia, University of California, San Francisco. Accepted for publication June 4, 1985.

Address correspondence to Dr. Rosen, Department of Anesthesia, University of California, San Francisco, Room S-436, Third and Parnassus Avenues, San Francisco, CA 94143.

© 1985 by the International Anesthesia Research Society

period of hypoxia and acidosis, sheep were injected intravenously over 10 sec with one of the following doses: 5.7 mg/kg of 2% lidocaine ($n = 5$); 11.4 mg/kg of 2% lidocaine ($n = 6$); 2.1 mg/kg of 0.75% bupivacaine ($n = 6$); or 4.2 mg/kg of 0.75% bupivacaine ($n = 6$). The doses were identical to those used in a previous study of bupivacaine-induced cardiac arrhythmias in nonacidotic sheep (1).

If the animals were feeding normally and were ambulatory, vigorous, and afebrile 24 hr after the first exposure to intravenous lidocaine or bupivacaine, they were studied again, using an alternate drug or dose. Not every animal was given all four doses of local anesthetics. Some animals were excluded from study when they developed pyrexia or pulmonary complications due to tracheostomies; others died before an alternate drug or dose could be given. The low doses were chosen to simulate accidental intravenous injection during epidural anesthesia in humans. Higher doses were selected to exaggerate the cardiac effects of such an injection.

After injection of bupivacaine or lidocaine, ventilation was discontinued for 90 sec and then resumed with an $F_{I_{O_2}}$ of 1.0 and a flow rate of 15 L/min to improve $Pa_{O_2}$ during resuscitation. Thiopental, 1 mg/kg, was given intravenously to terminate seizure activity that persisted more than 30 sec, monitored by the EEG.

To measure arterial blood gas tensions, acid–base status, and local anesthetic drug concentrations, we obtained baseline blood samples before and at 30 sec, and 1, 2, 3, 4, 5, 10, 15, 20, and 30 min after the injection of local anesthetic. Whole-blood drug concentrations were determined using a gas–liquid chromatographic technique. The concentrations of bupivacaine in whole blood were determined using a modification of the gas chromatographic method developed by Asling et al. (5). Cyclizine hydrochloride, 0.4 μg/ml, was used as the internal standard, and the concentrations of NaOH and HCl were 0.5N and 0.1N, respectively. The oven temperature was increased to 220° C. The extraction and concentration procedures used were those described by Asling et al. Surface and intracardiac ECG, EEG, and heart rate were recorded continuously. If cardiovascular collapse occurred, closed-chest cardiac compression and intravenous pharmacologic therapy (epinephrine, atropine, ephedrine, and calcium chloride) were administered according to the guidelines of the American Heart Association. Direct-current countershocks were given at 50–400 joules when ventricular fibrillation occurred. These resuscitative measures continued for 15–20 min.

For analysis of hemodynamic and ECG data, terms were defined as follows. Significant hemodynamic changes refers to changes in mean arterial pressure (MAP) of more than 50% after drug injection. Sinus rhythm exists when the baseline rhythm rate is within 25% of that before drug injection. Sinus bradycardia occurs when the baseline rhythm rate decreases more than 25% and QRS complexes are normal. Sinus tachycardia is said to have occurred when the baseline rhythm rate increases more than 25% and QRS complexes are normal. Atrioventricular conduction block is conduction of less than 1:1 between atria and ventricles, or no atrioventricular conduction in the presence of discernible atrial activity. A wide-QRS-complex rhythm is a rhythm lasting at least 10 sec or 10 beats with no discernible atrial activity preceding the QRS complex. Also, the duration of the QRS complex must be more than 100% greater than its baseline value, at a rate within 25% of control. Wide-QRS-complex bradycardia occurs when a wide-QRS-complex rhythm is accompanied by a rate decrease of more than 25% from baseline rate. Its opposite, wide-QRS-complex tachycardia, consists of wide-QRS-complex rhythm with a rate increase of more than 25% from baseline rate. Electromechanical dissociation is organized electrical activity with no pulsations visible during direct intraarterial tracing.

We compared data using analysis of variance and unpaired Student's *t*-test. A probability level of less than 0.05 was considered statistically significant.

## Results

There were no significant differences in animal weights among the four groups. All animals had EEG evidence of seizure activity within 30 sec of the intravenous injection of bupivacaine or lidocaine. Clinical seizure activity (convulsion) was suppressed by the prolonged action of succinylcholine in sheep. Approximately half of the animals in each group were given thiopental. Although thiopental, 1 mg/kg intravenously, usually terminated the seizure activity, on two occasions a second dose was required to end seizures.

At the time of injection, all animals were hypercarbic and moderately hypoxemic (Figs. 1–3). No significant differences existed among the four groups. During the 90 sec of apnea after injection, arterial blood gas tensions did not change significantly (Figs. 1–3).

Arrhythmias did not occur before the intravenous injection of either anesthetic or before onset of seizures. The ECG changes and rhythms, the incidence of significant hemodynamic changes (i.e., changes in MAP of at least 50%), and the incidence of death are

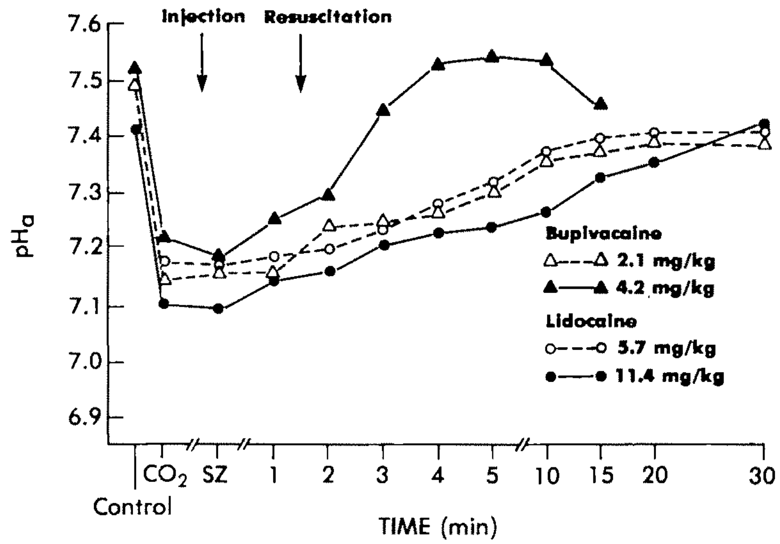


Figure 1. Change in arterial pH in sheep made hypoxic and hypercapnic and given lidocaine or bupivacaine intravenously at one of two dose levels. Abbreviations: $CO_2$, period of induced respiratory acidosis (hypercapnia); SZ, time of seizure. The times of drug injection and onset of resuscitation are shown.

shown in Table 1. Changes in heart rate and mean arterial blood pressure are shown in Figures 4 and 5. After administration of low-dose lidocaine, no animal ($n$ = 5) had significant hemodynamic change, and 4 of 5 animals had sinus tachycardia. After injection of high-dose lidocaine ($n$ = 6), 3 of 6 animals had a decrease in mean arterial blood pressure of over 50%: 1 had sinus tachycardia, and 2 remained in sinus rhythm. The three ewes with no significant hemodynamic changes developed sinus tachycardia.

In contrast, after administration of low-dose bupivacaine ($n$ = 6), 3 of 6 animals had significant hemodynamic changes, and all sheep had evidence of serious ECG changes or arrhythmias; one animal died. Animals given high-dose bupivacaine ($n$ = 6) also had evidence of serious ECG changes, and, despite vigorous resuscitative efforts, became hypotensive and died.

The most common abnormality after bupivacaine administration was wide-QRS-complex bradycardia, occurring in most animals regardless of dose. Many of the animals given bupivacaine had more than one type of arrhythmia. Two-thirds of the animals given high-dose bupivacaine had electromechanical dissociation and refractory asystole.

Ventilation with 12% carbon dioxide and air produced a significant increase in blood pressure (about 40%) in all animals in all groups, and a small but statistically insignificant increase in heart rate. After local anesthetic injection and subsequent resuscita-

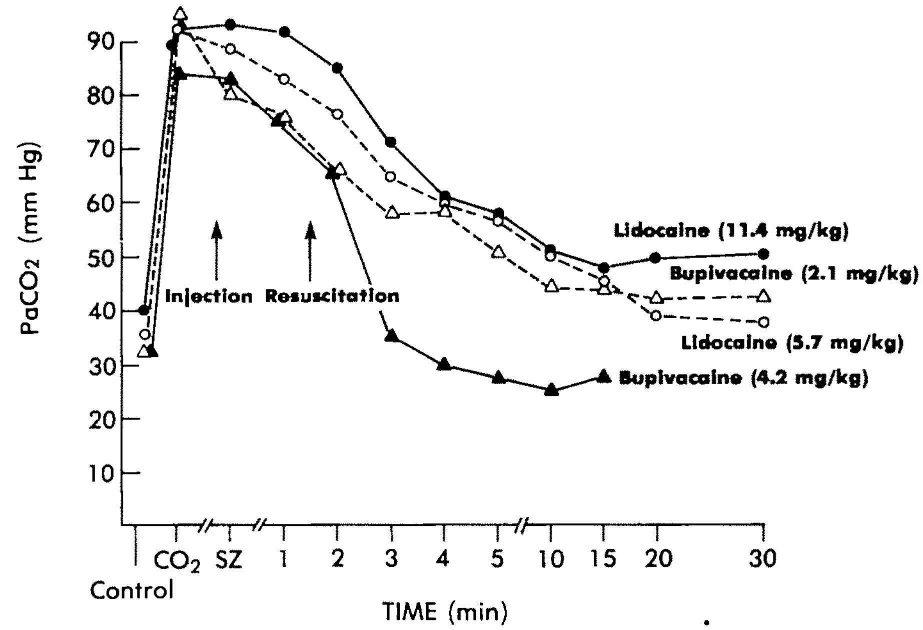


Figure 2. Change in $Pa_{CO_2}$ in sheep made hypoxic and acidotic with 12% $CO_2$ and given lidocaine or bupivacaine intravenously at one of two dose levels. Abbreviations: $CO_2$, period of induced respiratory acidosis (hypercapnia); SZ, time of seizure. The times of drug injection and onset of resuscitation are shown.

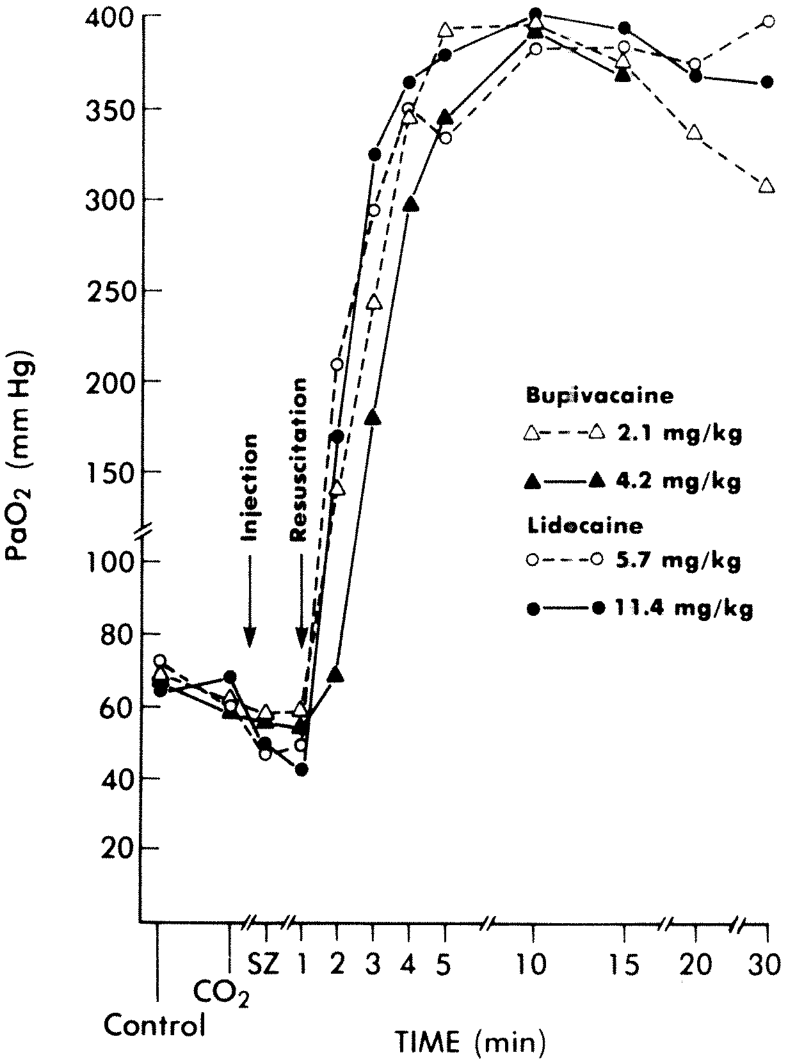


Figure 3. Change in $PaO_2$ in sheep made hypoxic and hypercapnic and given lidocaine or bupivacaine intravenously at one of two dose levels. Abbreviations: $CO_2$, period of induced respiratory acidosis (hypercapnia); SZ, time of seizure. The times of drug injection and onset of resuscitation are shown.

tion, MAP decreased as $PaCO_2$ was corrected with hyperventilation. During resuscitation, respiratory acidosis and hypoxemia were corrected rapidly. During the first 3 min after drug injection, there were no significant differences in arterial pH, $PCO_2$, or $PO_2$ among the animals in each of the four groups. After 3 min of resuscitation, all animals had a $PaO_2$ greater than 100 mm Hg (Fig. 3) and a pHa greater than 7.2 (Fig. 1). Significant metabolic acidosis did not occur in any group at any time. The greatest base deficit, 4.6 mEq/L, occurred in animals given the high dose of bupivacaine. After injections of high-dose bupivacaine, all animals were without systolic arterial pressure within 2 min as a result of electromechanical dissociation. After 3 min, the animals given high-dose bupivacaine had significantly higher arterial pH values and lower arterial $PCO_2$ values than did animals in the other three groups. This was associated with bicarbonate administration and ventilation, and inadequate circulatory support, with mean arterial pressures below 50 mm Hg during closed-chest massage. None of the animals requiring closed-chest cardiac massage survived.

The peak concentrations of anesthetic in blood occurred 30–60 sec after injection of either anesthetic (Figs. 6,7). The concentrations of lidocaine in blood for both high- and low-dose groups rapidly decreased to less than 7 μg/ml 5 min after injection (Fig. 6). The concentration of bupivacaine in blood, especially for the higher dose, remained in toxic ranges, above 2–3 μg/ml (6), for more than 15 min after injection (Fig. 7).

## Discussion

We found that intravenous bupivacaine, but not lidocaine, produced fatal cardiovascular collapse during moderate hypoxia and acidosis. Previous animal stud-

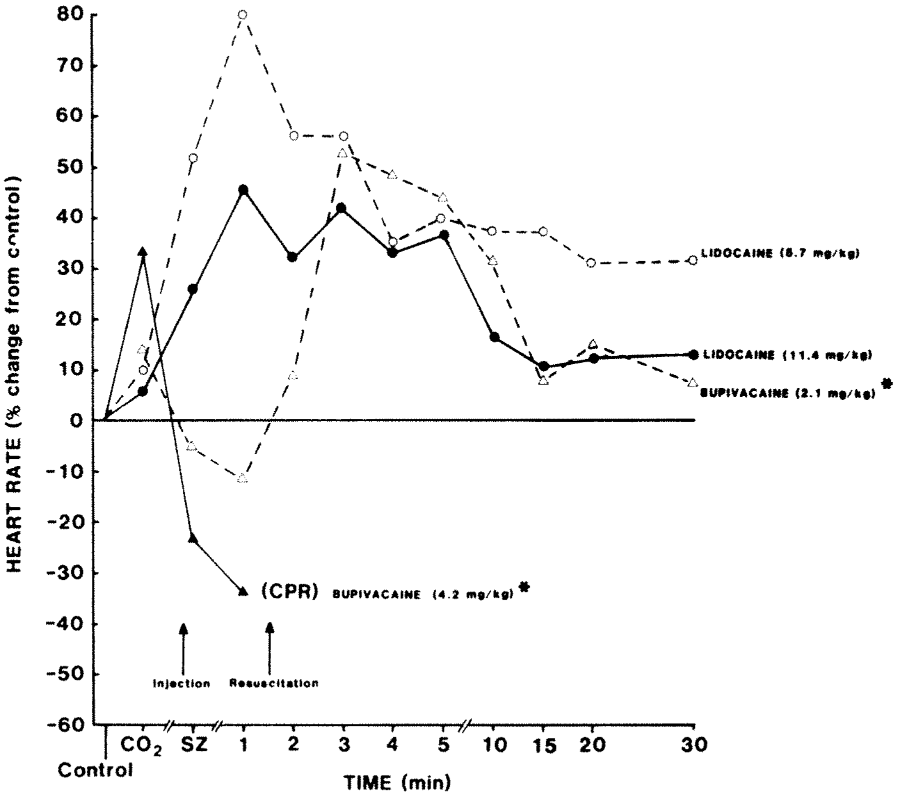


Figure 4. Change in heart rate in sheep made hypoxic and hypercapnic and given lidocaine or bupivacaine intravenously at one of two dose levels. Abbreviations: $CO_2$, period of induced respiratory acidosis (hypercapnia); SZ, time of seizure; *, one animal that received low-dose bupivacaine and all animals that received high-dose bupivacaine required cardiopulmonary resuscitation. The heart rate changes after onset of resuscitation are excluded for these animals. The times of drug injection and onset of resuscitation are shown.

Table 1. Significant Electrocardiographic Rhythms, Hemodynamic Changes, and Death—Incidence after Injection of Lidocaine or Bupivacaine at Two Dose Levels in Sheep (in%)

| | Lidocaine[a] | | Bupivacaine[b] | |
|---|---|---|---|---|
| | Low dose ($n$ = 5) | High dose ($n$ = 6) | Low dose ($n$ = 6) | High dose ($n$ = 6) |
| Significant hemodynamic changes | 0 | 50 | 50 | 100 |
| Sinus rhythm | 20 | 33 | 0 | 0 |
| Sinus bradycardia | 0 | 0 | 0 | 33 |
| Sinus tachycardia | 80 | 66 | 0 | 0 |
| Atrioventricular conduction block | 0 | 0 | 0 | 50 |
| Wide-QRS-complex rhythm | 0 | 0 | 33 | 50 |
| Wide-QRS-complex bradycardia | 0 | 0 | 50 | 83 |
| Wide-QRS-complex tachycardia | 0 | 0 | 0 | 17 |
| Electromechanical dissociation | 0 | 0 | 17 | 66 |
| Death | 0 | 0 | 17 | 100 |

[a] 2% lidocaine: low dose = 5.7 mg/kg; high dose = 11.4 mg/kg.
[b] 0.75% bupivacaine: low dose = 2.1 mg/kg; high dose = 4.2 mg/kg.

ies of bupivacaine cardiotoxicity have used a variety of experimental models and have produced conflicting results. De Jong et al. (7) found that bupivacaine, but not lidocaine, caused severe cardiac arrhythmias in cats infused with threshold-convulsant and supraconvulsant doses of local anesthetics. Sage et al. (8) found that in some unanesthetized dogs, severe cardiac arrhythmias occurred after a 30-sec intravenous administration of a convulsive dose of bupivacaine, and not lidocaine. However, Liu et al. (9) found that hemodynamic function deteriorated similarly as increasing doses of bupivacaine, lidocaine, etidocaine, prilocaine, or mepivacaine were administered to anesthetized and mechanically ventilated dogs. Liu et al. also compared threshold-convulsant doses of bupivacaine and lidocaine with doses required to produce toxic cardiovascular reaction in awake dogs and found that bupivacaine was no more toxic than lidocaine (10). Furthermore, when Munson et al. (11) evaluated bupivacaine-induced convulsions in subhuman primates, they observed no cardiac arrhythmias; their methods, however, differ from ours in that bupivacaine or lidocaine were infused relatively slowly, rather than injected rapidly, and animals were neither hypoxic nor acidotic.

Kotelko et al. (1) evaluated the effects of 10-sec infusions of bupivacaine and lidocaine in unanesthetized sheep ($n$ = 14). Although bupivacaine produced

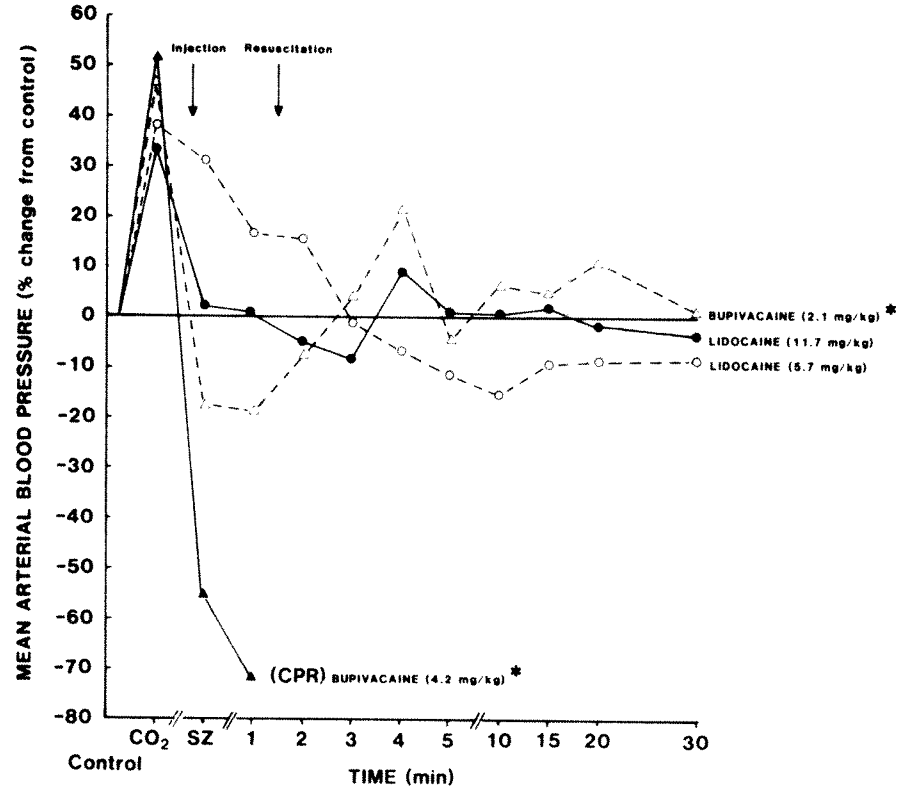


Figure 5. Change in mean arterial blood pressure in sheep made hypoxic and hypercapnic and given lidocaine or bupivacaine intravenously at one of two dose levels. Abbreviations: $CO_2$, period of induced respiratory acidosis (hypercapnia); SZ, time of seizure; *, one animal that received low-dose bupivacaine and all animals that received high-dose bupivacaine required cardiopulmonary resuscitation. The blood pressure changes after onset of resuscitation are excluded for these animals. The times of drug injection and onset of resuscitation are shown.

severe cardiac arrhythmias, severe hypoxia and acidosis did not occur, and none of the animals died. The lowest $PaO_2$ was 53 mm Hg, the highest $PaCO_2$ was 54 mm Hg, and the lowest pH was 7.36. We believe the relative absence of hypoxia and acidosis was significant.

Sage et al. (12), studying isolated bathed guinea pig atrial preparations, found that neither hypoxia nor metabolic or respiratory acidosis alone enhanced atrial depression caused by local anesthetics, whereas conditions simulating combined hypoxia/acidosis greatly enhanced bupivacaine-induced cardiac depression. In addition, Moore et al. (4) demonstrated that despite prompt ventilation and termination of local anes-

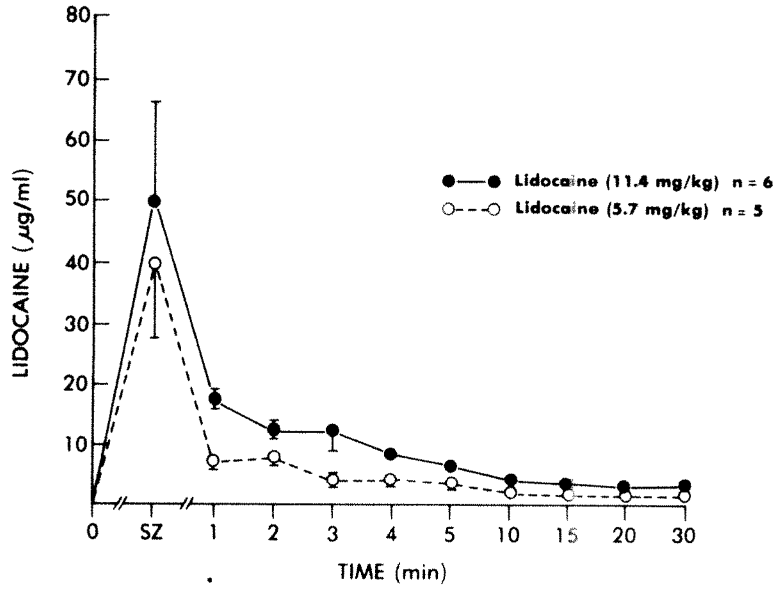


Figure 6. Change in whole-blood drug levels of lidocaine (mean ± SEM) in sheep made hypoxic and acidotic and given lidocaine intravenously at one of two dose levels. Abbreviations: SZ, time of seizure. Seizure occurred at a variable time after injection of lidocaine, but always prior to 1 min.

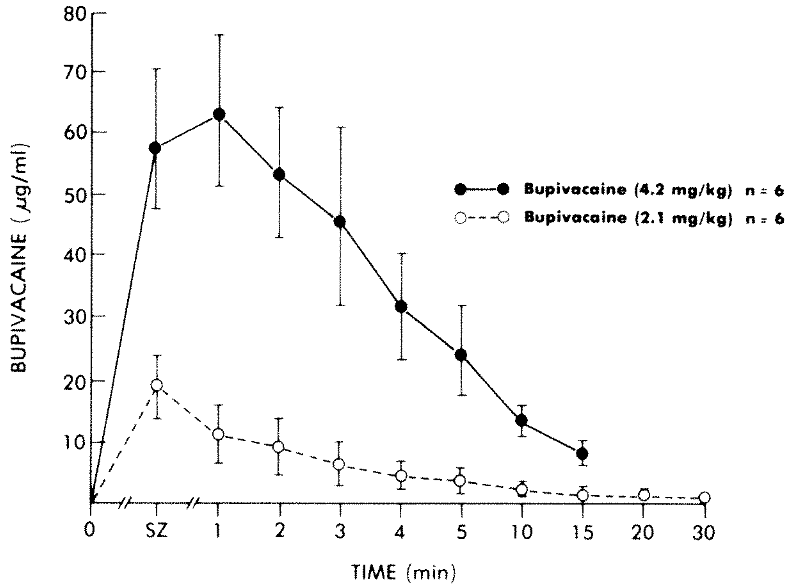


Figure 7. Change in whole-blood drug levels of bupivacaine (mean ± SEM) in sheep made hypoxic and acidotic and given bupivacaine intravenously at one of two dose levels. Abbreviations: SZ, time of seizure. Seizure occurred at a variable time after injection of bupivacaine, but always prior to 1 min.

thetic-induced convulsions, the development of severe hypoxia and acidosis in humans may be unavoidable. In two cases, they found that within 60 sec of seizure, $Pa_{O_2}$ decreased to as low as 33 mm Hg and pH to as low as 6.99, while $Pa_{CO_2}$ increased to as high as 76 mm Hg.

Our present study confirms previous work on the cardiotoxicity of bupivacaine and demonstrates that such toxicity is exacerbated when associated with hypoxia and acidosis, two conditions commonly occurring with local anesthetic-induced convulsions. In our previous study of awake, unanesthetized, normoxic, nonacidotic sheep given intravenous high-dose bupivacaine, serious ECG changes occurred: 80% of the animals had tachyarrhythmias described as ventricular tachycardia; 60% had atrioventricular blocks; and all had wide QRS complexes. Results from the present study demonstrate that hypoxic and acidotic animals given the same high doses of bupivacaine became hypotensive and demonstrated serious ECG changes that included wide-QRS-complex arrhythmias and electromechanical dissociation. P-waves on ECG were not always discernible with these wide-QRS-complex arrhythmias, and ventricular tachycardia could not be distinguished from supraventricular tachycardia with aberrant conduction. Different types of arrhythmias were found after the use of high-dose bupivacaine in the two studies; those in the present study may be attributable to the presence of acidosis and hypoxia. All previously studied normoxic, nonacidotic animals given high-dose bupivacaine ($n = 5$) survived; in the present study, all hypoxic, acidotic animals given this dose died.

Comparison of the concentration of local anesthetic in blood (using Student's unpaired $t$-test) of hypoxic, acidotic animals with the concentration obtained in normoxic, nonacidotic animals (1) revealed no significant differences for any group during the first 15 min after injection, with one exception: the high-dose bupivacaine group. In both studies, the first samples obtained after injection were drawn at the onset of seizure activity rather than at a fixed time after injection. Thus these samples were obtained at variable times dependent on the onset of EEG seizure activity, and consequently, may not represent peak blood levels. Also, the standard error for anesthetic concentrations measured in blood samples obtained at seizure onset is large. The overall higher levels of bupivacaine in blood samples of hypoxic, acidotic animals given high-dose bupivacaine probably results from decreased tissue perfusion and decreased drug uptake secondary to cardiovascular collapse.

Although our animal model attempted to mimic the reported clinical conditions of bupivacaine-induced cardiotoxicity, there are limitations to applying our data to humans. For example, although the cardiac conduction system in sheep may approximate that of humans, the systems are not identical. Furthermore, we induced hypoxia and acidosis before injecting local anesthetic, thereby possibly exaggerating adverse effects. Although case reports of fatal cardiac arrest in humans after accidental intravenous injection of bupivacaine have usually pertained to parturients, the present study does not address the relative effects of pregnancy on bupivacaine cardiotoxicity. Morishima et al. (13) found that pregnant sheep required a smaller dose of bupivacaine to produce cardiovascular depression than did nonpregnant animals. It is also not clear why peak bupivacaine blood concentrations were so much higher than peak lidocaine blood concentrations. This discrepancy may have resulted because cardiovascular collapse occurred immediately after bupivacaine administration, thereby producing poor tissue perfusion and decreased tissue uptake of bupivacaine.

A second limitation of this study is the possible inadequacy of the resuscitation provided. Using closed-chest massage, we were unable to maintain mean arterial pressures above 50 mm Hg, probably because of the anatomy of the sheep thorax. Possibly resuscitation and survival would have been more successful with open-heart massage. Kasten and Martin (14) reported successful resuscitation of dogs when using open cardiac massage to counteract the effects of a massive intravenous overdose of bupivacaine. However, prior to drug administration, they had performed a sternotomy and pericardotomy in the dogs to allow prompt access to the open heart.

Finally, the lack of randomization in this study may have biased the results. However, prior to each study, all animals appeared vigorous and unaffected by studies performed previously.

In summary, we believe the awake experimental model more closely simulates the clinical situation in which a local anesthetic is accidentally injected intravenously in humans, potentially producing a cardiotoxic response. A possible explanation for the observed cardiotoxity of bupivacaine compared with lidocaine has been offered by Clarkson and Hondeghem (15) who documented quantitative differences in properties of frequency-dependent block for the two anesthetics. Bupivacaine had an enhanced affinity for inactive sodium channels and a very slow dissociation rate from resting sodium channels. Substantial accumulation of block occurred at heart rates between 60–150 beats/min, compared with the diastolic recovery from block that occurred with lidocaine. Our data further demonstrate that bupivacaine is more cardiotoxic than lidocaine, and that in animals this toxicity is enhanced by the prior presence of hypercarbia, acidosis, and hypoxia.

The authors wish to express their gratitude to Judy Johnson and Merrilyn Jones for technical assistance, and to Ayerst Laboratories, Inc., for providing halothane.

## References

1. Kotelko DM, Shnider SM, Dailey PA, Brizgys RV, Levinson G, Shapiro WA, Koike M, Rosen MA. Bupivacaine-induced cardiac arrhythmias in sheep. Anesthesiology 1984;60:10–8.
2. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine (editorial). Anesthesiology 1979;51: 285–7.
3. Edde RR, Deutsch S. Cardiac arrest after interscalene brachial-plexus block. Anesth Analg 1977;56:446–7.
4. Moore DC, Crawford RD, Scurlock JE. Severe hypoxia and acidosis following local anesthetic-induced convulsions. Anesthesiology 1980;53:259–60.
5. Asling JH, Shnider SM, Wilkinson GR, Way EL. Gas chromatographic determination of mepivacaine in capillary blood. Anesthesiology 1969;31:458–61.
6. Scott DB. Evaluation of the toxicity of local anaesthetic agents in man. Br J Anaesth 1975;47:56–61.
7. DeJong RH, Ronfeld RA, DeRosa RA. Cardiovascular effects of convulsant and supraconvulsant doses of amide local anesthetics. Anesth Analg 1982;61:3–9.
8. Sage D, Feldman H, Arthur GR, Covino BG. Cardiovascular effects of lidocaine and bupivacaine in the awake dog. Anesthesiology 1983;59:A210.
9. Liu P, Feldman HS, Covino BM, Giasi R, Covino BG. Acute cardiovascular toxicity of intravenous amide local anesthetics in anesthetized ventilated dogs. Anesth Analg 1982;61:317–22.
10. Liu PL, Feldman HS, Giasi R, Patterson MK, Covino BG. Comparative CNS toxicity of lidocaine, etidocaine, bupivacaine, and tetracaine in awake dogs following rapid intravenous administration. Anesth Analg 1983;62:375–9.
11. Munson ES, Tucker WK, Ausinsch B, Malagodi MH. Etidocaine, bupivacaine, and lidocaine seizure thresholds in monkeys. Anesthesiology 1975;42:471–8.
12. Sage D, Feldman HS, Datta S, Covino B. Influence of lidocaine and bupivacaine on isolated guinea pig atria in the presence of acidosis and hypoxia. Anesth Analg 1984;63:1–7.
13. Morishima HO, Pedersen H, Finster M, Tsuji A, Hiraoka H, Feldman HS, Arthur GR, Covino BG. Is bupivacaine more cardiotoxic than lidocaine? Anesthesiology 1983;59:A409.
14. Kasten GW, Martin ST. Successful cardiovascular resuscitation after massive intravenous bupivacaine overdosage in anesthetized dogs. Anesth Analg 1985;64:491–7.
15. Clarkson CW, Hondeghem LM. Mechanism for bupivacaine depression of cardiac conduction: fast block of sodium channels during the action potential with slow recovery from block during diastole. Anesthesiology 1985;62:396–405.

ANESTH ANALG
1985;64:1097–100

# Age and the Solubility of Volatile Anesthetics in Ovine Tissues

Jerrold Lerman, MD, FRCP(C), George A. Gregory, MD, Mary M. Willis, BS,
Brigitte I. Schmitt, MD, and Edmond I. Eger II, MD

LERMAN J, GREGORY GA, WILLIS MM, SCHMITT BI, EGER EI II. Age and the solubility of volatile anesthetics in ovine tissues. Anesth Analg 1985;64:1097–100.

*To determine the effect of age on the solubility of volatile anesthetics in tissues, we measured the blood/gas and tissue/gas partition coefficients of isoflurane, enflurane, halothane, and methoxyflurane in vitro at 37°C in newborn lambs and postpartum adult sheep. The tissue specimens examined were brain, heart, liver, kidney, muscle, and fat. Hematocrit and serum concentrations of albumin, globulin, cholesterol, and triglycerides were measured. The blood/gas partition coefficients, hematocrit, and the serum concentrations of albumin, globulin, cholesterol, and triglycerides in the newborn lambs did not differ from those in the adult sheep. The tissue/blood partition coefficients [the ratio of (tissue/gas)/(blood/gas)] in newborn lambs were 28% [mean value for the four anesthetics] less than those in the adults. The tissue/blood partition coefficients for enflurane and methoxyflurane in newborn tissues were significantly less ($P < 0.05$) than those for halothane and isoflurane. We conclude that the blood/gas partition coefficients in sheep do not change significantly with age, that the tissue/blood partition coefficients in sheep increase with age, and that the time required for equilibration of volatile anesthetics (particularly enflurane and methoxyflurane) in newborn tissues is probably less than in adult sheep.*

Key Words: ANESTHETICS, VOLATILE—enflurane, halothane, isoflurane, methoxyflurane. AGE—adult, newborn. SOLUBILITY—blood, tissue.

The rate of increase in alveolar anesthetic partial pressure is more rapid in infants and children than in adults (1,2). This more rapid increase has been attributed to a greater ratio of alveolar ventilation to functional residual capacity, a greater fraction of the cardiac output perfusing the vessel-rich tissues (1,2), a greater alveolar ventilation and cardiac output per kg body mass, and significantly lower blood/gas partition coefficients (3) in newborns than in adults. Another possible explanation, however, may be a difference in the solubility of volatile anesthetics in newborn tissues. Cook et al. (4) found that the concentration of halothane in the brain of the newborn rat was less than that of the more mature adult rat. These investigators attributed this difference to an increased water content in the brain of the newborn rat. Widdowson (5) reviewed age-dependent changes in the concentrations of brain constituents in humans: the concentration of cholesterol was lower and the water content higher in the brains of newborns than in the brains of adults. Therefore, the solubility of volatile anesthetics in brain and other tissues might increase with age. Such an increase would explain the more rapid rate of increase in alveolar anesthetic partial pressure in infants and children than in adults.

To determine the effect of age on the solubility of volatile anesthetics in tissues, we measured the blood/gas and the tissue/gas partition coefficients of isoflurane, enflurane, halothane, and methoxyflurane in the brain, heart, liver, kidney, muscle, and fat in newborn lambs and adult sheep.

## Methods

Blood and tissue specimens were obtained from seven healthy newborn lambs (less than 7 days of age and weighing less than 5 kg) and six postpartum adult sheep (within 3 days after parturition). Fifteen ml of blood were aspirated from an indwelling arterial or venous catheter and divided into an 8-ml anticoagulated (with EDTA) specimen for determination of hematocrit and blood/gas partition coefficients, and a 7-ml clotted specimen for determination of serum concentrations of albumin, globulin, cholesterol, and triglycerides. After blood was collected, animals were

---

Supported in part by NIH Grant 1 PO1 AG 03104-02. Received from the Departments of Anesthesia and Pediatrics, and the Cardiovascular Research Institute, University of California, San Francisco. Dr. Lerman is the recipient of a fellowship in anesthesia and pharmacology from The Hospital for Sick Children Foundation, Toronto Ontario, Canada. Accepted for publication May 6, 1985.

Address correspondence to Dr. Eger, Department of Anesthesia, HSE 1386, University of California, San Francisco, CA 94143.

© 1985 by the International Anesthesia Research Society

anesthetized with intravenous pentobarbital and killed. Tissue specimens were removed from the brain (mixture of grey and white matter), heart (lateral free-wall of the left ventricle), kidney (renal cortex), liver (parenchyma), muscle (quadriceps), and fat (perirenal or omentum). To minimize variability in tissue/gas partition coefficients, we carefully collected the tissue specimens from comparable areas of organs in each animal. Each tissue specimen was dissected from the organ, and the capsule and fascia were removed. Blood was expelled from each specimen, and the blood vessels were dissected and removed from the specimen.

The tissue specimens were prepared for measurement of the tissue/gas partition coefficients immediately after collection. (A small number of specimens was refrigerated in normal saline for 18 hr before analysis. This had no effect on the solubility determinations.) The volume of each tissue specimen was measured by saline volume displacement. Each specimen was then homogenized in a volume of saline (0.9% sodium chloride) equal to three times the volume of the specimen, using a mini-cup Waring blender (20,000 rpm). The homogenate was filtered through a $\frac{1}{16}$-in$^2$ aluminum mesh screen to remove extraneous fascia, which spuriously decreases the tissue/gas partition coefficient by increasing the volume of homogenate and by contributing its very low anesthetic solubility. The net volume of tissue present in the homogenate was determined as being the difference between the volume of the tissue specimen and the volume of extraneous fascia (measured by saline volume displacement). These refinements in tissue preparation were performed to minimize variability in the partition coefficient determinations in tissue specimens from different sheep.

Blood/gas and tissue/gas partition coefficients were determined by equilibrating 2–3 ml of blood or homogenate with 15 ml of a mixture of anesthetic gases (isoflurane, enflurane, halothane, and methoxyflurane) in a silicone-greased glass syringe. The syringe was incubated in a water bath at 37°C for 2 hr and shaken vigorously as described previously (6).

After 2 hr of incubation, we measured the concentrations of anesthetics in the gas phase using gas chromatography. We determined the concentrations of anesthetics in the homogenate phase by aspirating an aliquot of homogenate into an evacuated flask, dissipating the vacuum with air, and equilibrating the contents of the flask at 37°C for 1 hr as described previously (6). The tissue/gas partition coefficient, derived from a mass balance wherein the anesthetic content of the homogenate is equal to the sum of the anesthetic contents of the tissues and saline, is expressed as follows:

$$\lambda_T = \lambda_H + \frac{V_S}{V_T}(\lambda_H - \lambda_S) \qquad (1)$$

where $\lambda_T$, $\lambda_H$, and $\lambda_S$ are the tissue/gas, homogenate/gas, and saline/gas partition coefficients, respectively; and $V_T$ and $V_S$ are the volumes (ml) of tissue and saline, respectively. The saline/gas partition coefficient for each anesthetic was determined previously (6). The tissue/blood partition coefficient for each tissue was determined to be the ratio of the tissue/gas and blood/gas partition coefficients.

The serum concentrations of albumin, globulin, cholesterol, and triglycerides were measured in both newborn lambs and adult sheep.

Statistical significance ($P < 0.05$) was determined using the Bonferonni *t*-test (7), one-way analysis of variance, and the Student–Newman–Keuls test (8).

## Results

The mean blood/gas partition coefficients for newborn lambs did not differ significantly from those for adult sheep (Table 1). The tissue/blood partition coefficients for newborns and adults in all of the tissues except fat ranged from 1.05 to 3.11. Tissue/blood partition coefficients were 28% (mean value) lower in newborn tissues than in adult sheep (Table 1). Tissue/blood partition coefficients for newborn brain, heart, liver, and kidney were significantly lower for enflurane and methoxyflurane than for isoflurane and halothane. The tissue/blood partition coefficients for newborn muscle were significantly lower for enflurane and methoxyflurane than for halothane. The tissue/blood partition coefficients for newborn fat were significantly lower for enflurane than for isoflurane and halothane. The tissue/blood partition coefficients for adult tissues did not differ among the anesthetics.

Because fat samples from the adult sheep could not be homogenized satisfactorily, fat/gas partition coefficients were not determined for adult sheep. The mean hematocrit and serum concentrations of albumin, globulin, cholesterol, and triglycerides in newborn lambs did not differ significantly from those in adult sheep (Table 2).

## Discussion

The tissue/blood partition coefficients in sheep are in close agreement with previous results (9). The differences in tissue/blood partition coefficients among the four anesthetics did not parallel the differences in either blood/gas partition coefficients or lipid solubility of the four anesthetics. Although only a small

Table 1. Mean Blood/Gas and Tissue/Blood Partition Coefficients in Newborn Lambs and Adult Sheep

| Partition coefficients | Isoflurane | Enflurane | Halothane | Methoxyflurane |
|---|---|---|---|---|
| Blood/gas | | | | |
| Newborn | 1.22 ± 0.09 | 1.71 ± 0.14 | 2.35 ± 0.16 | 14.2 ± 1.2 |
| Adult | 1.41 ± 0.11 | 1.73 ± 0.10 | 2.46 ± 0.16 | 14.6 ± 0.43 |
| Tissue/blood | | | | |
| Brain | | | | |
| Newborn | 1.45 ± 0.26 | 1.10 ± 0.16 | 1.61 ± 0.22[a] | 1.16 ± 0.30[a] |
| Adult | 2.10 ± 0.90 | 1.52 ± 0.44 | 2.39 ± 0.29[a] | 1.81 ± 0.08[a] |
| Heart | | | | |
| Newborn | 1.89 ± 0.15 | 1.42 ± 0.13[a] | 1.85 ± 0.16 | 1.22 ± 0.16[a] |
| Adult | 2.27 ± 0.55 | 1.83 ± 0.28[a] | 2.17 ± 0.32 | 1.64 ± 0.13[a] |
| Liver | | | | |
| Newborn | 1.84 ± 0.15[a] | 1.46 ± 0.17[a] | 1.97 ± 0.16[a] | 1.56 ± 0.12[a] |
| Adult | 3.11 ± 0.75[a] | 2.37 ± 0.47[a] | 3.04 ± 0.78[a] | 2.39 ± 0.49[a] |
| Kidney | | | | |
| Newborn | 1.29 ± 0.11[a] | 1.05 ± 0.14[a] | 1.30 ± 0.12[a] | 1.10 ± 0.13 |
| Adult | 1.79 ± 0.25[a] | 1.41 ± 0.08[a] | 1.72 ± 0.22[a] | 1.21 ± 0.08 |
| Muscle | | | | |
| Newborn | 1.55 ± 0.23 | 1.19 ± 0.17 | 1.71 ± 0.41 | 1.22 ± 0.36 |
| Adult | 2.18 ± 0.67 | 1.61 ± 0.61 | 2.24 ± 0.85 | 1.96 ± 0.79 |
| Fat | | | | |
| Newborn | 32.3 ± 3.7 | 24.9 ± 3.5 | 34.5 ± 3.7 | 28.8 ± 6.0 |

Data are means ± SD.

[a] $P < 0.05$ between newborn lambs and adult sheep.

The mean blood/gas and tissue/blood partition coefficients for newborn lambs and adult sheep at 37°C. The tissue/blood partition coefficients in newborn lambs were 28% less than those in adult sheep. The fat/blood partition coefficients for adult sheep were not determined. The tissue/blood partition coefficients for enflurane and methoxyflurane in newborns were significantly less than those for isoflurane and halothane ($P < 0.05$) (see text).

number of sheep was studied in each group, approximately half of the tissue/blood partition coefficients measured in newborn lambs were significantly lower than those in adult sheep. It is likely that a larger proportion of the tissue/blood partition coefficients would have been significantly different had more sheep been studied. Tissue/blood partition coefficients increase with age.

In a previous study, we found a significant difference with age in the blood/gas partition coefficients in humans (3). We attributed this difference to parallel changes in the concentrations of serum constituents with age. However, in the present study, blood/gas partition coefficients in newborn lambs did not differ significantly from those in adult sheep. This was not surprising because the concentrations of serum constituents in newborn lambs did not differ significantly from those in adult sheep (Table 2).

Results for the tissue/blood partition coefficient determinations in postpartum adult sheep may underestimate the partition coefficients in nonpregnant adult sheep. Because the tissue/blood partition coefficient is the ratio of the tissue/gas and blood/gas partition coefficients, changes in either the tissue/gas or blood/gas partition coefficient may affect the tissue/blood partition coefficient. The serum triglyceride concentrations in the postpartum adult sheep were 10% of those for nonpregnant adult sheep (10,11). Although this should decrease the blood/gas partition coefficient, the effect is likely to be small (3). The effect of pregnancy on salt and water retention may be of greater importance. In pregnant humans, salt and water retention increases the blood volume and decreases the serum albumin concentration (12,13). If similar changes were also true for sheep, then this may reduce the blood solubility of anesthetics in postpartum sheep. The net effect of the lower triglyceride concentration and increased salt and water content should result in minimal changes in the blood/gas partition coefficients in postpartum sheep. Water retention during pregnancy might also increase the water content of tissues. This would decrease the tissue/gas partition coefficient and lead us to underestimate the actual tissue/blood partition coefficient for nonpregnant adult sheep. This latter hypothesis may explain in part, the small differences in tissue/blood partition coefficients between newborn lambs and postpartum adult sheep in this study (Table 1).

This study demonstrated that volatile anesthetics are less soluble in tissues of newborn lambs than in tissues of adult sheep (Table 1). The reduced tissue/blood partition coefficients in newborn lambs decrease the tissue capacity for anesthetics and thereby shorten the time constant for anesthetic equilibration in the tissues. As a consequence, the rate of increase of the partial pressure of anesthetics in tissues might

Table 2. Blood Chemistry for Newborn Lambs and Adult Sheep

| | Newborn lambs | Adult sheep |
|---|---|---|
| Hematocrit (vol%) | 35 ± 11 | 34.5 ± 5 |
| Serum concentrations | | |
| Albumin (gm/dl) | 2.77 ± 0.24 | 3.26 ± 0.63 |
| Globulin (gm/dl) | 3.17 ± 1.6 | 3.43 ± 0.85 |
| Cholesterol (mg/dl) | 92.9 ± 38 | 69.0 ± 19 |
| Triglyceride (mg/dl) | 25.3 ± 21 | 7.0 ± 4.9 |

Data are means ± SD. The hematocrit and serum constituent concentrations in newborn lambs were not significantly different from those in adult sheep. The serum concentrations of albumin and globulin were less, whereas those of cholesterol and triglycerides were greater in the newborn lambs than in the adult sheep.

be more rapid in newborn lambs than in adult sheep. Based on these differences in solubility, one might also predict that the rate of increase in alveolar anesthetic partial pressure in newborn lambs would be more rapid than in adult sheep. If this difference in anesthetic solubility with age were also true in human tissues, it would be consistent with previous studies reporting a more rapid increase in alveolar anesthetic partial pressure in infants and children than in adults (1,2). It would follow, therefore, that the reduced solubility of volatile anesthetics in the tissues of newborn lambs may explain, in part, the more rapid rate of increase in alveolar anesthetic partial pressure in infants and children than in adults.

For newborn tissues, tissue/blood partition coefficients were significantly lower for enflurane than for isoflurane and halothane. As a result, the rate of increase in the partial pressures of anesthetics in newborn tissues would be expected to be greater for enflurane than for isoflurane and halothane. This, together with the relatively small blood/gas partition coefficient for enflurane, supports the observation that enflurane equilibrates rapidly in the alveolae and furthermore suggests that it may equilibrate more rapidly in the tissues than either isoflurane or halothane.

The clinical importance of this effect of age on the rate of increase in alveolar and tissue anesthetic partial pressures varies for the four volatile anesthetics. If alveolar ventilation and cadiac output are held constant, then the effect of age on differences in the tissue/blood partition coefficient and, therefore, on the rate of increase in anesthetic partial pressure would depend on the relative magnitude of the blood/gas and tissue/blood partition coefficients. For example, if the tissue/blood partition coefficient of a poorly soluble anesthetic increased, then the rate of increase in tissue anesthetic partial pressure may slow. However, this effect on the rate of increase in alveolar anesthetic partial pressure would be minimal. In contrast, if the tissue/blood partition coefficient of a more soluble anesthetic increased, not only would it slow the rate of increase in tissue anesthetic partial pressure but it also would compound the effect of the increased blood/gas partition coefficient. The result would be a slowing of the rate of increase in alveolar anesthetic partial pressure. Thus the clinical significance of changes in the tissue/blood partition coefficients may be more evident for the more soluble volatile anesthetics.

## References

1. Salanitre E, Rackow H. The pulmonary exchange of nitrous oxide and halothane in infants and children. Anesthesiology 1969;30:388–94.
2. Brandom BW, Brandom RB, Cook DR. Uptake and distribution of halothane in infants: in vivo measurements and computer simulations. Anesth Analg 1983;62:404–10.
3. Lerman J, Gregory GA, Willis MM, Eger EI II. Age and solubility of volatile anesthetics in blood. Anesthesiology, 1984;61:139–43.
4. Cook DR, Brandom BW, Shiu G, Wolfson B. The inspired median effective dose, brain concentration at anesthesia, and cardiovascular index for halothane in young rats. Anesth Analg 1981;60:182–5.
5. Widdowson EM. Changes in body proportions and composite during growth. In: Davis JA, Dobbing J, eds. Scientific foundations of pediatrics. Philadelphia:WB Saunders, 1974:153–63, 750–4.
6. Lerman J, Willis MM, Gregory GA, Eger EI II. Osmolarity determines the solubility of volatile anesthetics in aqueous solutions at 37°C. Anesthesiology 1983;59:554–8.
7. Glantz SA. Primer of biostatistics. New York:McGraw-Hill, 1981:87–8.
8. Zar JH. Biostatistical analysis. New Jersey:Prentice-Hall, 1974: 133–9, 151–5.
9. Eger EI II. Anesthetic uptake and action. Baltimore:Williams and Wilkins, 1974:80–3, 160–9.
10. Mitruka BM, Rawnsley HM. In: Clinical biochemical and hematological reference values in normal experimental animals. New York:Masson Publishers USA INC., 1977:168–70.
11. Altman PL, Dittmer DS, eds. In: Biology data book. Second edition, volume III. Maryland:Federation of the American Societies of Experimental Biology, 1974:1961–3, 1970.
12. Metcalfe J, McAnulty JH, Ueland K. Cardiovascular physiology. In: Clinical obstetrics and gynecology. Philadelphia: Harper & Row, 1981:694–6.
13. DeAlvarez RR, Afonso JF, Sherrard DJ. Serum protein fractionation in normal pregnancy. Am J Obstet Gynecol 1961, 82:1096–111.

# A Double-Blind Comparison of Multiple Intramuscular Doses of Ciramadol, Morphine, and Placebo for the Treatment of Postoperative Pain

W. Forrest Powell, MD

POWELL WF. A double-blind comparison of multiple intramuscular doses of ciramadol, morphine, and placebo for the treatment of postoperative pain. Anesth Analg 1985;64:1101–7.

*Ciramadol, an agonist–antagonist analgesic (in intramuscular doses of 30 and 60 mg) was compared with 10 mg of morphine and placebo in a double-blind, parallel study in 160 patients with postoperative pain. The patients were assigned randomly to one of the four treatment groups and could receive a dose of the medication every 3 hr as needed for 48 hr; a maximum of six doses was allowed in a 24-hr period. Formal efficacy assessments using standard pain intensity and pain relief scales were restricted to the initial dose period. The three active therapy groups had significantly ($P < 0.05$) higher analgesia scores than the placebo group on all efficacy scales. The mean cumulative efficacy scores for the initial dose evaluation were highest for 60 mg of ciramadol; however, patients' overall evaluations of therapy were highest in the morphine group. Nausea and vomiting were the most frequent adverse experiences (15–25% incidence); however, there were no statistically significant differences between groups in their occurrence. A greater percentage ($P < 0.05$) of patients reported skin reactions in the 60 mg ciramadol group (15%) than in the 30 mg ciramadol (0%) and placebo (0%) groups. Sedation was slightly higher with the active therapies than with placebo. Changes in vital signs were minimal. It is concluded that 60 mg of ciramadol compares favorably with 10 mg of morphine as a postoperative analgesic.*

Key Words: ANALGESICS—ciramadol. PAIN—postoperative.

The demonstration that certain drugs could antagonize the effects of narcotics as well as produce analgesia led to the development of narcotics with mixed agonist–antagonist activity as potentially nonaddicting analgesics (1). Ciramadol, [1*R*-[1α(*R**), 2α]]-3-[(dimethylamino)-(2-hydroxycyclohexyl)methyl]phenol, hydrochloride, is one of the new analgesics in the class of partial agonists. It is not related chemically to the narcotics (Fig. 1). In laboratory animals, ciramadol was shown to be an effective analgesic when administered orally or parenterally and to have narcotic antagonist activity that is slightly less than that of nalorphine (2).

Ciramadol is nonconstipating in laboratory animals, and studies of human colonic myoelectric activity have demonstrated that ciramadol does not produce narcotic-like effects on the colon (unpublished observations). The drug's effects on cardiovascular and respiratory functions have been minimal in dogs (3) and in humans (unpublished observations), and animal studies suggest that ciramadol has a low potential for addiction and dependence (unpublished observations). In humans, ciramadol is rapidly absorbed after oral administration or intramuscular injection, with approximately 80 and 96%, respectively, available to the systemic circulation (4). Urinary excretion of ciramadol and its conjugated metabolites accounts for nearly all of the drug given (4). Its elimination half-life is 4–5 hr (4,5).

The results of early clinical trials suggested that 20–60-mg doses of orally administered ciramadol were effective in the treatment of chronic pain due to cancer (6,7). Subsequently, oral doses of 90 mg of ciramadol were shown to be superior to 60 mg of codeine for the relief of cancer pain (8). The analgesic effects of 15–60 mg oral doses of ciramadol also have been demonstrated in the treatment of postepisiotomy and postoperative pain (9–12). In addition, the incidence of side effects reported in these studies has been low.

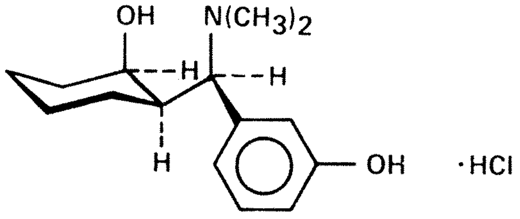
---

Supported by grants from Wyeth Laboratories, Philadelphia, Pennsylvania. All study drugs were provided by Wyeth Laboratories, Philadelphia, Pennsylvania.

Received from the Department of Anesthesiology, University of Tennessee Memorial Hospital and Research Center, Knoxville, Tennessee. Accepted for publication June 6, 1985.

Address correspondence to Dr. Powell, 651 Arrowhead Trail, Knoxville, TN 37919.

© 1985 by the International Anesthesia Research Society



**CIRAMADOL**

[1R-[1α(R*),2α]]-3-[(dimethylamino)-(2-hydroxycyclohexyl)methyl]phenol, hydrochloride

Figure 1. Chemical structure of ciramadol.

The findings of an open, uncontrolled study suggested that 20 mg of ciramadol, administered intravenously, could provide relief of severe pain due to renal colic (13). Other results indicated that a 30-mg dose of intramuscular ciramadol was equivalent to 10 mg of morphine for the relief of postoperative pain (personal communication, F. Camu, Department of Anesthesia, Academisch Ziekenhuis, Vrije Universiteit Brussel, Brussels, Belgium). A similar investigation in postoperative pain, however, failed to show an analgesic response with either 30- or 60-mg doses of intramuscularly administered ciramadol (14).

The present multiple-dose study was designed to evaluate further the relative analgesic potency of these two doses of intramuscularly administered ciramadol by comparison with morphine and placebo.

## Methods

### *Study Design*

This four-group parallel study was conducted in a double-blind fashion. The participants were 160 patients who experienced moderate or severe pain after surgery. Candidates for inclusion in the study were male or female patients of any race who were 18–65 yr of age, weighed between 100 and 210 lb, and were classified as ASA physical status I or II as defined by the American Society of Anesthesiologists. Patients excluded were those who had a history of chronic analgesic or tranquilizer use or drug dependence, were sensitive to narcotics or narcotic antagonists, had received analgesics within 3 hr or psychotropic medication within 6 hr of the administration of the study medication, were taking interfering or potentially interacting medications, or were unable to communicate meaningfully regarding their pain. Pregnant women and women who were breast-feeding were excluded also. Each patient gave written consent before participating, and approval for this investigation was granted by the hospital's research review committee.

The patients underwent general surgical, orthopedic, or gynecologic operations. There were no restrictions on the drugs used for anesthesia. For most procedures, anesthesia was induced by intravenous thiopental and was maintained by various inhalation anesthetic agents supplemented by skeletal muscle relaxants, barbiturates, and narcotics.

After surgery, the patients were randomly assigned to receive one of the following drug treatments: 30 mg of ciramadol; 60 mg of ciramadol; 10 mg of morphine; or placebo. The study medications were provided in individual patient packages containing identical-appearing 2-ml ampules. Drugs were administered by intramuscular injection every 3 hr, as needed, for 48 hr. No more than six doses were given during a 24-hr period. The injection site was alternated between right and left deltoid muscles.

### *Drug Assessments*

Efficacy assessments were made by the physician or nurse observer, using standard analgesia scales, immediately before, at 15 and 30 min, and at 1, 2, 3, 4, 5, and 6 hr after administration of the first dose of study medication. Categorical ratings of none [0], mild [1], moderate [2], or severe [3] were used to describe pain intensity. In addition, the patients rated pain intensity using a linear analog scale by placing a mark on a 100-mm line; pain was evaluated relative to the opposite extremes of the line, which represented "no pain" and "worst pain ever felt." Pain relief was judged as one of the following: pain got worse [−1], no relief [0], a little relief [1], moderate relief [2], a lot of relief [3], or complete relief [4].

Pain intensity differences (PID) and pain analog intensity difference (PAID) scores were derived by subtracting the pain intensity ratings at each observation from the corresponding baseline ratings. Cumulative PID and PAID scores were calculated by multiplying the scores at each evaluation by the fraction of an hour since the last observation and then adding these weighted scores to obtain the summed pain intensity differences (SPID) and summed pain analog pain intensity differences (SPAID). Similarly, total pain relief (TOTPAR) scores were obtained by adding the weighted pain relief scores at each observation.

During the initial dose evaluation, patients not receiving adequate pain relief and requesting additional medication for pain were given a second dose of the study medication, provided they did not ask to withdraw from the study. Patients who required additional analgesic medication before the end of the 6-hr period were considered treatment failures and were assigned efficacy scores corresponding to their baseline pain intensity and to no pain relief after remedication according to the method advocated by Lasagna (15) and Houde et al. (16).

At each observation, the degree of sedation (i.e., none, mild, moderate, or marked) and vital signs were recorded by the observer. All adverse experiences were recorded as they emerged and were rated by the investigator as definitely, probably, possibly, or not related to the drug treatments. Laboratory tests including hematologic studies, blood chemistry, and standard urinalysis were done before the start of the study and repeated within 24 hr after the patient either completed or withdrew from the study. The injection sites were examined for reaction at 30 min and 24 hr after injection.

As each patient completed treatment, he or she was asked to rate the overall drug experience as excellent [4], good [3], fair [2], or poor [1]. The investigator also rated each patient's overall response to treatment as satisfactory or unsatisfactory based on the onset and duration of analgesia and the side effect profile.

### *Statistical Analysis*

Demographic variables and baseline ratings of a continuous nature were compared using a one-way analysis of variance supplemented by the Student–Newman–Keuls test for pairwise comparisons (17). Nominal variables and categorized baseline scores were compared by the $\chi^2$ and Fisher's exact tests (18). Categorized efficacy and posttreatment sedation scores were analyzed by the generalized Cochran–Mantel–Haenszel procedure using marginal ridit scores with baseline pain intensity as a covariable (19,20). The PAID scores, vital signs, and laboratory results were compared among the groups by a one-way analysis of covariance with the baseline level as the covariate; vital signs and laboratory determinations were examined for changes within groups from baseline by the paired *t*-test. The frequencies of adverse experiences were compared among treatment groups by the $\chi^2$ test, supplemented by Fisher's exact test for pairwise comparisons.

All statistical tests were based on two-tailed alternative hypotheses, and an observed difference was declared to be statistically significant if the test result indicated that the probability of obtaining a difference of this magnitude or larger due to chance (i.e., under the null hypothesis) was 0.05 or less.

## Results

There were 40 patients in each of the four drug treatment groups; however, one patient from each of the two ciramadol groups and one from the morphine group had received meperidine less than 3 hr before the study medication and were excluded from the efficacy analysis. One patient in the 60 mg ciramadol group who was heavily sedated when the test medication was administered was excluded also. All patients were included in the safety evaluation.

Most of the patients were women (81%) and the majority of the patients were white (88%). The mean age was 33 yr (range 18–65 yr) and mean weight was 64.6 kg (range 44–90 kg). Nearly equal numbers of patients reported initial (baseline) pain intensity as moderate ($n = 78$) or severe ($n = 82$), and most patients (93%) reported either mild or no sedation at baseline. No statistically significant differences in demographic or baseline data were found among the groups.

Because of the lack of independence among observations, aggregative effect of multiple doses, and discontinuations of patients with unsatisfactory responses, formal assessment of analgesia was made only during the 6 hr after the initial dose of study medication.

Table 1 presents the mean PID and PAID scores obtained during the initial dose evaluation. Throughout this 6-hr period, mean scores on the three primary efficacy scales (PID, PAID, and pain relief) were higher in the active treatment groups than in the placebo group. On all three scales, the highest mean scores, which indicate greater analgesia, were seen in the 60 mg ciramadol group and the 10 mg morphine group; at 2 hr and beyond, mean scores were higher with 60 mg of ciramadol than with morphine. Generally, mean scores with 30 mg of ciramadol were slightly lower than those with 10 mg of morphine, although the former were consistently higher than those obtained with placebo.

At the 1-hr observation, the mean efficacy scores peaked at similar levels for the 60 mg ciramadol and 10 mg morphine groups. For the 30 mg ciramadol group, the mean scores generally were below those obtained with 60 mg of ciramadol and 10 mg of morphine and reached their peak levels between 30 min and 2 hr. The mean scores in the placebo group peaked at much lower levels at 30 min.

PID and PAID scores in the 60 mg ciramadol group were significantly higher than those in the placebo group at nearly every observation throughout the 6 hr. In the 30 mg ciramadol and morphine groups these scores were significantly higher than in the placebo

Table 1. Differences in Pain Intensity From Baseline

| Time after therapy | Ciramadol (30 mg) | Ciramadol (60 mg) | Morphine (10 mg) | Placebo |
|---|---|---|---|---|
| | | Mean PID Scores[a] | | |
| 15 min | 0.7[b] | 0.6[b] | 0.6[b] | 0.2 |
| 30 min | 0.9[b] | 1.3[b] | 1.3[b] | 0.4 |
| 1 hr | 0.9[b] | 1.6[b] | 1.5[b,c] | 0.3 |
| 2 hr | 1.0[b] | 1.4[b] | 1.1[b] | 0.2 |
| 3 hr | 0.8[b] | 1.1[b] | 0.8[b] | 0.2 |
| 4 hr | 0.5[b] | 0.8[b] | 0.5[b] | 0.1 |
| 5 hr | 0.3 | 0.6[b] | 0.4 | 0.2 |
| 6 hr | 0.3 | 0.4 | 0.3 | 0.1 |
| | | Mean PAID Scores[a] | | |
| 15 min | 18.6[b] | 19.3[b] | 21.7[b] | 7.3 |
| 30 min | 27.3[b] | 34.4[b] | 37.6[b] | 13.6 |
| 1 hr | 24.4[b] | 41.7[b,c] | 42.8[b,c] | 9.6 |
| 2 hr | 26.0[b] | 36.7[b] | 32.3[b] | 7.8 |
| 3 hr | 19.8[b] | 27.6[b] | 24.9[b] | 4.2 |
| 4 hr | 15.5[b] | 18.4[b] | 17.5[b] | 2.6 |
| 5 hr | 8.0 | 13.9 | 12.5 | 4.3 |
| 6 hr | 8.0 | 12.3[b] | 8.3 | 1.1 |

[a] Higher scores indicate greater pain relief.
[b] Significantly ($P < 0.05$) higher than placebo.
[c] Significantly ($P < 0.05$) higher than 30 mg of ciramadol.

group from 15 min through 4 hr. Occasionally, PID and PAID scores in the 60 mg ciramadol and the morphine groups were significantly above those in the 30 mg ciramadol group. The pain relief scale yielded similar results; pain relief scores in the 30 and 60 mg ciramadol groups and the morphine group were significantly higher than scores in the placebo group from 15 min through 4 hr after drug administration.

As shown in Figure 2, the cumulative efficacy scores (SPID, SPAID, and TOTPAR) at 6 hr were consistently highest with 60 mg of ciramadol, followed by 10 mg of morphine, 30 mg of ciramadol, and then the placebo. The scores on these three measurements of analgesia were significantly higher in the 60 mg ciramadol and 10 mg morphine groups than in the placebo group. In addition, the 6-hr SPAID scores with 60 mg of ciramadol were significantly better than those with 30 mg.

Effective pain relief, i.e., a pain relief score of moderate or greater, was reported at some time during the initial dose period by 76% of the patients treated with 60 mg of ciramadol, 72% of those treated with 30 mg of ciramadol, 82% of those treated with 10 mg of morphine, and 35% of the placebo-treated patients. Figure 3 compares the percentages of patients reporting effective pain relief at each observation for the four treatment groups. By the first evaluation (15 min) and for the duration of the 6-hr observation period, greater percentages of patients reported effective pain relief with the three active treatments than with placebo. The differences between active treatments and placebo were statistically significant from 15 min through 4 hr and at 6 hr in the 60 mg ciramadol and morphine groups and at 15 min through 4 hr in the 30 mg ciramadol group. With the exception of the 1-hr observation period, the reports of effective pain relief were consistently highest in the 60 mg ciramadol group; however, the differences between 60 mg of ciramadol and the other two active therapies were not statistically significant.

By 6 hr after the initial dose, a second dose of study medication or a standard analgesic medication had been requested by 55% of the patients in the 60 mg ciramadol group, 56% of the patients in the 30 mg ciramadol group, 49% of the patients in the morphine group, and 90% of those in the placebo group (Table 2). The cumulative remedication rates at the end of the initial dose observation period were significantly lower in the active therapy groups than in the placebo group. For the entire study period (maximum of 48 hr), the percentages of patients who withdrew from the study because of unsatisfactory pain relief were 38% in the 30 mg ciramadol group, 23% in the 60 mg ciramadol group, 13% in the morphine group, and 63% in the placebo group. The differences between active therapies and placebo in the percentages of patients who withdrew because of unsatisfactory pain relief were statistically significant. Also, a significantly

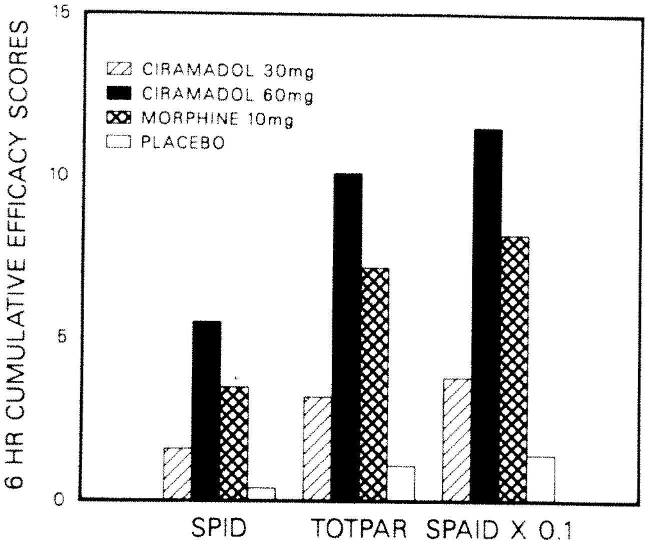


Figure 2. Cumulative efficacy scores (SPID, TOTPAR, SPAID × 0.1) at 6 hr after the initial dose of study medication. Higher scores indicate greater pain relief.

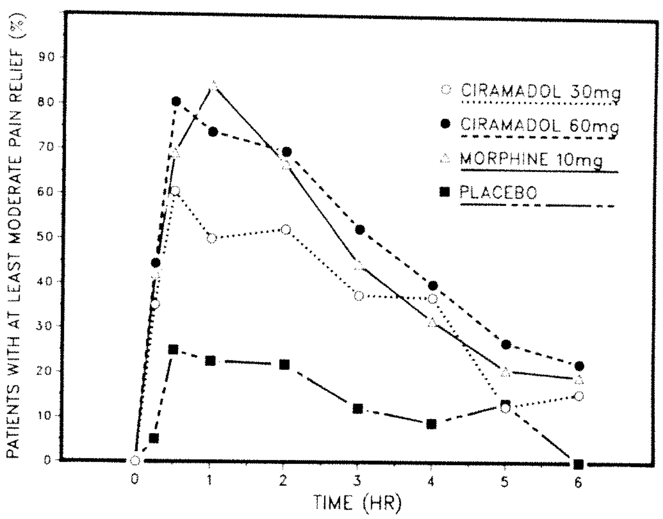


Figure 3. Percentage of patients reporting at least moderate pain relief during the initial dose (6-hr) evaluation.

higher percentage in the 30 mg ciramadol group than in the morphine group withdrew because of inadequate pain relief.

The mean number of doses received by patients in each of the four treatment groups was 4.6 in the 10 mg morphine group, 2.9 in the 60 mg ciramadol group, and 2.6 in both the 30 mg ciramadol and placebo groups. Although receiving fewer doses could in some cases be associated with a longer duration of analgesic effect, in this study the primary association seemed to be with an earlier pattern of withdrawal from the study.

The mean sedation scores at baseline were similar in the four treatment groups, with approximately 90% of the patients in each group reporting either no sedation or only mild sedation. After administration of the initial dose of study medication, the degree of sedation increased in each of the four treatment groups. In the active treatment groups, however, sedation scores increased slightly more than in the placebo group, with mean ratings in the range of mild to moderate. Frequently during the first hour, the degree of sedation was significantly higher with the active therapies than with placebo.

During the initial dose period and for the entire study, nausea and vomiting were the most frequently reported adverse experiences. At some time during the study, these effects were reported by eight (20%) patients in the 30 mg ciramadol group, 10 (25%) in the 60 mg ciramadol group, six (15%) in the morphine group, and seven (18%) in the placebo group. Adverse experiences affecting the skin (i.e., irritation at the injection site, pruritus, or rash) were reported by six (15%) patients receiving 60 mg of ciramadol, two (5%) receiving morphine, and none of the patients receiving 30 mg of ciramadol or placebo. The only statistically significant difference among the groups for the entire study was in the proportions with adverse experiences broadly categorized as those affecting the skin; significantly different pairwise differences were seen between the 60 mg ciramadol group and both the placebo and the ciramadol 30 mg groups.

In general, side effects were judged to be either mild or moderate; however, two patients reported severe adverse experiences. One patient in the 30 mg ciramadol group had severe nausea after the sixth injection of medication and was withdrawn from the study. One patient receiving placebo had severe hiccups (along with moderate nausea) and was withdrawn from the study.

During the initial dose period, statistically significant mean decreases in vital signs (3 to 9 mm Hg in systolic blood pressure, 2 to 4 mm Hg in diastolic blood pressure, 2 to 3 heartbeats/min, 1 to 3 breaths/min) were noted within active therapy groups. Differences among groups, however, were rarely statistically significant, and none of these changes were considered to be clinically significant.

In the observer's clinical evaluation, the test medication was rated as satisfactory for 62% of the patients in the 30 mg ciramadol group, 66% of the patients in the 60 mg ciramadol group, 85% of the patients in the morphine group, and 28% of the patients in the placebo group. Overall, ratings of good or excellent were given by 62% of the patients treated with 30 mg of ciramadol, 71% of the patients treated with 60 mg of

Table 2. Summary of Cumulative Remedication Rates—Initial Dose Period

| Time after therapy | Placebo ($n$ = 40) | Ciramadol (30 mg) ($n$ = 39) | Ciramadol (60 mg) ($n$ = 38) | Morphine (10 mg) ($n$ = 39) |
|---|---|---|---|---|
| 15 min | 0.0% | 0.0% | 0.0% | 0.0% |
| 30 min | 27.5% | 12.8% | 7.9% | 5.1% |
| 1 hr | 55.0% | 23.1% | 13.2% | 10.3% |
| 2 hr | 62.5% | 28.2% | 21.1% | 15.4% |
| 3 hr | 75.0% | 35.9% | 26.3% | 23.1% |
| 4 hr | 77.5% | 48.7% | 31.6% | 43.6% |
| 5 hr | 87.5% | 53.8% | 47.4% | 46.2% |
| 6 hr | 90.0% | 56.4% | 55.3% | 48.7% |

ciramadol, 85% of the patients treated with morphine, and 26% of the placebo treated patients. Overall ratings by both the physician and patients were significantly better for the three active therapies than for the placebo. In addition, patient ratings were significantly higher in the morphine group than in either of the ciramadol groups.

## Discussion

In this study, 30- and 60-mg doses of intramuscularly administered ciramadol and 10 mg of morphine were significantly more effective than placebo for the treatment of moderate to severe postoperative pain. In addition, 60 mg of ciramadol was equivalent to 10 mg of morphine for onset, duration, and level of peak effectiveness of analgesia. Although patient overall ratings of therapy were more favorable for morphine than for either 30 or 60 mg of ciramadol, the mean cumulative measures of pain relief and pain intensity differences from baseline at the end of the initial 6-hr evaluation were highest in the 60 mg ciramadol group.

It is important that no dysphoria or hallucinations were noted in any patients in this study. Nausea, occasionally associated with retching and vomiting, was the most frequently reported adverse experience in each of the four treatment groups, and in many cases it had occurred intermittently in the early postoperative period before study drug administration. Adverse experiences affecting the skin, which included mild burning after injection in a few cases or an occasional complaint of itching or rash, disappeared either spontaneously after several hours or after antihistamine therapy. The mild sedation associated with the active treatments was not considered to be a clinical disadvantage because many patients prefer sedation with analgesia during the first 24–48 hr after major surgery. The slight depression of respiratory rate, pulse, and blood pressure also was considered to be not clinically significant.

The efficacy results from the initial dose evaluation period in the present study are not consistent with the findings of an earlier investigation that evaluated single doses of these four drugs under a similar protocol (14). Based on their earlier findings, those authors conclude that ciramadol, at 30- or 60-mg doses, was ineffective as an analgesic in comparison with 10 mg of morphine. They suggest that narcotic antagonist effects may have contributed to the lack of a significant overall analgesic response in the groups receiving ciramadol and refer in particular to the experiences of some of their patients who had received ciramadol within 3–7 hr after a narcotic. Interestingly, these investigators point out that early analgesic trials with nalbuphine and butorphanol in postoperative pain were conducted in patients who were not given other narcotics during the perioperative period.

In contrast the results of the present study show dose-related analgesia with ciramadol in postoperative patients, all of whom had received narcotic analgesics either intraoperatively or postoperatively before receiving the study medication. The median time between the last dose of a narcotic analgesic and the administration of the test medication was similar in the four treatment groups, varying between 5.25 and 6 hr. It is possible that the amount of narcotic medication given prior to administration of the study drugs may have contributed to the disparity between the results of this and the earlier report. For example, the majority of patients in the present study were given the study drug on the day of surgery after receiving only one or two doses of a narcotic analgesic and all patients were essentially pain free preoperatively. In the earlier investigation, study medication was not administered until the first or second postoperative day.

However, based on the present findings, we conclude that intramuscularly administered ciramadol is an effective analgesic and that 60 mg of ciramadol compares favorably with 10 mg of morphine as an analgesic for the treatment of patients with moderate to severe postoperative pain. Further clinical investigation of ciramadol appears to be warranted.

The author wishes to acknowledge G. S. Littman, PhD, for the statistical analyses.

## References

1. Martin WR. History and development of mixed opioid agonists, partial agonists and antagonists. Br J Clin Pharmacol 1979;7:273S–9S.
2. Yardley JP, Fletcher H, Russel PB. A potent benzylamine analgesic: (−)cis-2(a-dimethylamino-m-hydroxybenzyl) cyclohexanol. Experientia 1978;34:1124–5.
3. Lewis AJ, Kirchner T. A comparison of the cardiorespiratory effects of ciramadol, dezocine, morphine and pentazocine in the anesthetized dog. Arch Int Pharmacodyn Ther 1981; 250:73–83.
4. Locniskar A, Lasseter KC, Freeland GR, Greenblatt DJ. Pharmacokinetics and bioavailability of ciramadol, a new analgesic. Clin Res 1983;31:630A.
5. Sisenwine SF, Cesario TO, Bauer J, Freeland G, Ruelius HW. The metabolic disposition of oral $^{14}$C-ciramadol in humans. Proceedings of the II World Conference on Clinical Pharmacology and Therapeutics. Washington, DC: American Society For Pharmacology and Experimental Therapeutics, 1983:77.
6. Cochrane AD, Bell R, Sullivan JR, Shaw J. Ciramadol, a new analgesic. Med J Aust 1979;2:501–2.
7. Staquet MJ. Analgesic effect of ciramadol in patients with chronic pain. Curr Med Res Opin 1980;6:475–7.
8. Stambaugh JE, McAdams J, Freeland G. Comparison of the analgesic efficacy and safety of oral ciramadol (Ciradol) to codeine and placebo in patients with chronic cancer pain. Clin Pharmacol Ther 1983;33:198.
9. Bloomfield SS, Sinkfield A, Mitchell J, Bichlmeir G, Barden TP. Ciramadol (Wy-15,705) and codeine analgesia after episiotomy. In: Harris LS, ed. Problems of drug dependence, 1982, NIDA Research Monograph 43. Maryland: Office of Science, NIDA;1983:224–30.
10. Fragen RJ, Caldwell NJ. Comparison of three doses of oral ciramadol and placebo for the treatment of moderate to severe postoperative pain. J Clin Pharmacol 1982;22:459–65.
11. Camu F. Double-blind comparison of the analgesic response to oral ciramadol (Wy-15,705) and pentazocine in post-operative pain. Eur J Clin Pharmacol 1981;19:259–62.
12. Defoort P, Thiery M, Martens G, Van Maele G. Double-blind trial of single-dose ciramadol for the treatment of post-episiotomy pain. Curr Med Res Opin 1983;8:481–6.
13. Oosterlinck W, Minnaert H. An open comparative trial of three doses of ciramadol used intravenously in renal colic. Curr Med Res Opin 1982;8:290–3.
14. Fragen RJ, Kouzmanoff C, Caldwell NJ. Intramuscularly administered ciramadol for management of postoperative pain: a comparative study. J Clin Pharmacol 1983;23:219–26.
15. Lasagna L. The evaluation of analgesic compounds in patients suffering from postoperative pain. In: Lasagna L, ed. International encyclopedia of pharmacology and therapeutics, section 6. New York, NY: Pergamon Press, 1966:51–8.
16. Houde RW, Wallenstein SL, Beaver WT. Evaluation of analgesics in patients with cancer pain. In: Lasagna L, ed. International encyclopedia of pharmacology in therapeutics, section 6. New York, NY: Pergamon Press, 1966;59–97.
17. Steel RGD, Torrie JH. Principles and procedures of statistics. New York, NY: McGraw Hill Book Company, 1960.
18. Sokal RR, Rohlf FJ. Biometry. San Francisco, CA: W. H. Freeman, 1969.
19. Landis JR, Cooper MM, Kennedy T, Koch GG. A computer program for testing average partial association in three-way contingency tables (PARCAT). Proceedings of the Statistical Computing Section of the American Statistical Association. Chicago, IL: American Statistical Association, 1977:157–62.
20. Landis JR, Heyman ER, Koch GG. Average partial association in three-way contingency tables: a review and discussion of alternate tests. Int Statist Rev 1978;46:237–54.

ANESTH ANALG
1985;64:1108–12

# Continuous Monitoring of Arterial Oxygen Saturation with Pulse Oximetry during Transfer to the Recovery Room

I.L. Tyler, MD, PhD, Boonrak Tantisira, MD, Peter M. Winter, MD, and
Etsuro K. Motoyama, MD

TYLER IL, TANTISIRA B, WINTER PM, MOTOYAMA EK. Continuous monitoring of arterial oxygen saturation with pulse oximetry during transfer to the recovery room. Anesth Analg 1985;64:1108–12.

*The incidence of hypoxemia in the immediate postoperative period was determined using a pulse oximeter for continuous monitoring of arterial oxygen saturation ($Sa_{O_2}$) in 95 ASA class I or II adult patients breathing room air during their transfer from the operating room to the recovery room. Hypoxemia was defined as 90% $Sa_{O_2}$ (arterial oxygen partial pressure ($Pa_{O_2}$) $\cong$ 58 mm Hg). Severe hypoxemia was defined as 85% $Sa_{O_2}$ ($Pa_{O_2} \cong 50$ mm Hg). Hypoxemia occurred in 33 (35%) patients; severe hypoxemia occurred in 11 (12%). Postoperative hypoxemia did not correlate significantly with anesthetic agent, age, duration of anesthesia, or level of consciousness. There was a statistically significant correlation ($P < 0.05$) between hypoxemia and obesity. All three patients with a history of mild asthma became severely hypoxemic even though none had perioperative evidence of obstructive disease, also a statistically significant ($P < 0.003$) finding.*

Key Words: HYPOXIA—postoperative. OXYGEN—postoperative blood levels.

It has long been accepted that air is an inappropriate breathing mixture for anesthetized patients (1,2). The 20.9% oxygen in ambient air is insufficient to provide a margin of safety against hypoxia, because lung function almost always deteriorates during the course of surgery and anesthesia. This deterioration may be due to decreased functional residual capacity (FRC) and increased airway closure, a ventilation/perfusion imbalance, or the development of atelectasis (3). Further, $CO_2$ retention caused by hypoventilation can in turn cause hypoxia by displacing oxygen from the alveoli, but this is important only when inspired air is not oxygen-enriched. Although moderate, transient decreases in the arterial oxygen partial pressure ($Pa_{O_2}$) may be acceptable in young, healthy patients, they certainly are not acceptable in patients with ischemic vascular disease.

In light of these concerns, it has been our longstanding practice to administer no less than 30% oxygen to patients under general anesthesia and to provide supplemental oxygen to all patients in the recovery room. However, healthy patients are frequently allowed to breathe room air during transfer from the operating room (OR) to the postanesthesia recovery room (PAR). This is at a time when ventilation is likely to be depressed from residual inhalation anesthetics or narcotics and when muscle relaxants have only recently been antagonized. Furthermore it is known that equilibration of $Pa_{O_2}$ with inspired gas mixtures takes about 30 sec even in normal volunteers (4), whereas patient transfer can take several minutes. Thus preoxygenation, even of a patient with an acceptable minute ventilation, does not guarantee normoxia during his or her transfer while breathing room air if there is an excessive aveolar–arterial oxygen pressure gradient ($A{-}aD_{O_2}$).

There is a surprising lack of data on patient oxygenation during postoperative transfer, explainable in part by the difficulty of measuring blood gases under such conditions. Recently, a rapid-response, battery-operable pulse oximeter (Nellcor Pulse Oximeter Model N-100, Hayward, CA 94545) became commercially available. We used this instrument to monitor arterial oxygen saturation ($Sa_{O_2}$) continuously in patients during their transfer from the OR to the PAR and determined the incidence and predictors of hypoxemia.

---

Received from the Department of Anesthesiology and Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania. Accepted for publication May 15, 1984.

Address correspondence to Dr. Tyler, Department of Anesthesiology, Magee-Women's Hospital, Forbes Avenue and Halket Street, Pittsburgh, PA 15213.

© 1985 by the International Anesthesia Research Society

Table 1. Incidence of Hypoxemia during Transfer in Relation to Primary Anesthetic Agent

| Primary agent[a] | Number of patients | Number with hypoxemia | % with hypoxemia | Number with severe hypoxemia | % with severe hypoxemia |
|---|---|---|---|---|---|
| Isoflurane | 51 | 20 | 39 | 4 | 7.8 |
| Enflurane | 19 | 7 | 37 | 4 | 21.1 |
| Fentanyl | 5 | 1 | 20 | 1 | 20.0 |
| Halothane | 3 | 0 | 0 | 0 | 0 |
| Morphine | 6 | 2 | 33 | 1 | 16.7 |
| Sufentanil | 11 | 3 | 27 | 1 | 9.1 |
| Total | 95 | 33 | 35 | 11 | 12 |

No statistically significant difference in the incidence of hypoxemia among the various agents was noted using the exact probability test.

[a] All anesthetics also included nitrous oxide.

## Methods

The study was approved by the Human Experimentation Committee of Magee-Women's Hospital. Over a 5-week period, we studied a sample of ASA class I and II adult patients who were scheduled for elective surgery under general anesthesia and who, in the opinion of the attending anesthesiologist, did not need supplemental oxygen during postoperative transfer. Obesity did not exclude a patient from the study. Patients who were hypothermic or shivering at the end of surgery were excluded. Because we were interested in the incidence of hypoxemia under routine conditions, we did not control the choice of anesthetic technique.

Immediately before being moved from the OR table to the stretcher for transfer to the PAR, each patient was given 100% oxygen; those with intubated tracheas were "sighed" to an airway pressure of 50 cm $H_2O$ for 5 sec. Patients continued to breathe 100% oxygen until the attending anesthesiologist was satisfied that the patient was ready for transfer. All patients spontaneously breathed 100% oxygen for at least 5 min after anesthetic agents had been discontinued and before the start of transfer. During this 5-min period, the probe of a pulse oximeter was clipped to the patient's thumb or finger. The supplemental oxygen was removed, the patient's level of consciousness was scored (0, unresponsive; 1, arousable; 2, awake), and transfer began. The time between the start of spontaneous breathing of room air and the lowest $SaO_2$ or 85% $SaO_2$ ($PaO_2 \cong 50$ mm Hg, using Nunn's nomogram and assuming normal acid–base balance and normal oxygen–hemoglobin affinity), whichever came first, was measured by the investigator with a stopwatch. If $SaO_2$ decreased to 85%, 100% oxygen was supplied via bag and valve. On arrival in the PAR, all patients were given 40% oxygen by mask or T-piece.

Unless stated otherwise, Student's *t*-test was used in the statistical analysis of continuous variables and the $\chi^2$-test was used for discrete variables. Data are reported as mean ± SD. *P* values $< 0.05$ were considered statistically significant.

## Results

All but two of the 95 patients studied were female. They had a mean age of 41 yr, with a range of 21–76. Body weights ranged from 0.9–2.64 times the Davidson standard (5) of ideal weight for height (men, ideal weight (lb) = 106 + ([height (in) − 60] × 6); women, ideal weight (lb) = 100 + ([height (in) − 60] × 5)). The mean duration of anesthesia was 108 ± 70 min, with a range of 15–310 min. All the common inhalation agents, as well as morphine and sufentanil, were represented in our sample (Table 1). The surgical procedures were primarily gynecologic or lower abdominal; none involved the thorax. Patients were under the care of any one of seven anesthesiologists.

The data are summarized in Tables 1–4. In all patients $SaO_2$ was 97% or higher during the period of spontaneous respiration of 100% oxygen before transfer. The incidence of hypoxemia during transfer, which we defined as an $SaO_2$ of 90% ($PaO_2 \cong 58$ mm Hg) or less, was 35%. The incidence of severe hypoxemia, which we defined as an $SaO_2$ of 85% ($PaO_2 \cong 50$ mm Hg), was 12%. One hypoxemic patient and one severely hypoxemic patient were coughing, but the remainder had no respiratory irregularity. The time from discontinuation of 100% oxygen to 85% $SaO_2$ was highly variable, with a mean of 155 ± 74 sec. When 100% oxygen was given during transfer to patients who became severely hypoxemic, $SaO_2$ rapidly rose to above 90%. In patients who did not become hypoxemic, the mean low value was 94.9% ± 2.3% ($PaO_2 \cong 73$ mm Hg). The low values occurred in a mean of 196 ± 67 sec. There was no statistically significant difference in the incidence of hypoxemia as a function of an-

Table 2. Variables for Patients Who Became Severely Hypoxemic during Transfer

| Patient number | Age (yr) | Fraction of ideal weight | Smoking (packs/day) | Primary agent | Time to 85% $Sa_{O_2}$ (sec) | Anesthesia time (min) | Level of consciousness[a] |
|---|---|---|---|---|---|---|---|
| 1 | 37 | 1.64 | | isoflurane | 160 | 30 | 1 |
| 2 | 41 | 0.98 | | enflurane | 210 | 40 | 0 |
| 3 | 24 | 1.57 | 0.5 | enflurane | 205 | 125 | 2 |
| 4 | 40 | 1.41 | | isoflurane | 183 | 185 | 0 |
| 5[b] | 35 | 1.40 | | enflurane | 30 | 35 | 1 |
| 6 | 38 | 1.75 | 1.5 | isoflurane | 56 | 120 | 1 |
| 7 | 56 | 2.26 | | enflurane | 103 | 205 | 0 |
| 8[c] | 41 | 1.30 | | morphine | 290 | 310 | 1 |
| 9[c] | 34 | 1.63 | | sufentanil | 150 | 195 | 1 |
| 10 | 56 | 1.29 | | fentanyl | 125 | 110 | 1 |
| 11[c] | 24 | 1.33 | 1.5 | isoflurane | 195 | 90 | 2 |

[a] 0, unresponsive; 1, arousable; 2, awake.

[b] Patient 5 began coughing just before the hypoxemic episode. None of the other patients had any respiratory irregularity during transfer.

[c] Patients 8, 9, and 11 had a history of mild asthma without hospitalization. None had experienced an asthma attack within the past six months. None had signs or symptoms of asthma or obstructive disease perioperatively.

Table 3. Variables for Hypoxemic and Nonhypoxemic Patients[a]

| | Number of patients | Age (yr) | Fraction of ideal weight | Anesthesia time (min) | Minimum oxygen saturation (%) | Time to minimum saturation (sec) | Level of consciousness[b] |
|---|---|---|---|---|---|---|---|
| Severely hypoxemic | 11 | 39 ± 10 | 1.50 ± 0.30 | 131 ± 86 | 85[c] | 155 ± 74[c] | 0.91 ± 0.70 |
| Hypoxemic | 33 | 43 ± 14 | 1.52 ± 0.38 | 113 ± 72 | 85[c] | —[c] | 0.93 ± 0.69 |
| Nonhypoxemic | 62 | 40 ± 15 | 1.16 ± 0.21 | 110 ± 74 | 94.9 ± 2.3 | 196 ± 67 | 0.79 ± 0.71 |

[a] Mean ± SD.

[b] Average ± SD of 0, unresponsive; 1, arousable; 2, awake.

[c] Patients whose oxygen saturation reached 85% were immediately given oxygen to avoid more profound hypoxemia. Times recorded were those at which saturation reached 85%.

esthetic agent (by exact probability test), patient age, duration of anesthesia, history of smoking, or level of consciousness. The mean fraction of ideal weight—1.52 ± 0.38 for hypoxemic patients; 1.16 ± 0.21 for nonhypoxemic—was a significant ($P < 0.05$) predictor of hypoxemia. In patients in whom $Sa_{O_2}$ did not reach 85%, there was a significant correlation ($P < 0.001$) between minimum $Sa_{O_2}$ and body weight (Table 4).

Three patients had a history of mild asthma. None had been hospitalized or received emergency room treatment for asthma, nor had they had an asthma attack within the past 6 months. None had signs or symptoms of asthma or obstructive disease perioperatively. All three became severely hypoxemic (Table 2, footnote *c*). This was statistically significant ($P < 0.003$) by the exact probability test.

## Discussion

Postoperative hypoxemia occurs commonly and has been documented even after minor procedures under general anesthesia (6). Many studies have described its evolution over hours to days. Significant correlations of slowly developing postoperative hypoxemia have been shown with duration of anesthesia (7), site of surgical incision (8), age (9), obesity (10), and pain (11). Nitrous oxide diffusion hypoxia was studied extensively a decade or more ago. Sheffer et al. (12), for example, measured blood–gas tensions at 30-sec intervals after the discontinuation of nitrous oxide and the substitution of room air. During the first 2.5 min, $Pa_{O_2}$ decreased rapidly to a mean of 54.3 ± 11.2 mm Hg, after which it rapidly recovered. But there have been few investigations of hypoxemia during the first few postoperative minutes—that is, immediately after nitrous oxide has presumably been washed out. Virtue et al. (13) measured blood–gas tensions in samples drawn at 5-min intervals postoperatively. Despite the fact that these observations were made in Denver, at an altitude of roughly 5000 ft, they found only a 19% incidence of hypoxemia. We know of no study in which continuous measurements of $Sa_{O_2}$ were made to assess oxygenation during transfer from the OR to the PAR.

Table 4. Correlation Between Minimum Saturation and Other Variables for Patients in whom $Sa_{O_2}$ Did Not Decrease Below 85%

| | Fraction of ideal weight | Age | Anesthesia time |
|---|---|---|---|
| Minimum $Sa_{O_2}$ | 0.448[a] | −0.159[b] | −0.159[b] |

[a] $P < 0.001$.
[b] $P > 0.05$.

Our study was made feasible by the recent commercial availability of a noninvasive, portable, battery-operable pulse oximeter. This instrument determines absolute arterial oxygen saturation by taking the ratio of only the pulsatile (thus arterial) component of the transmittance of two wavelengths of light. One wavelength is strongly absorbed by oxygenated and the other by reduced hemoglobin. The oximeter updates the averaged $Sa_{O_2}$ reading every 5 sec. The accuracy and limitations of this oximeter have been documented previously (14), along with cautions necessary to avoid erroneous readings. We adhered to these. In addition, we used a heavy, multiple-use probe, which effectively filtered out the vibrations caused by bed movement; these vibrations otherwise could have been interpreted by the oximeter as arterial pulsations.

Our intention in this study was to determine the incidence of hypoxemia during postanesthetic management as routinely practiced. Thus one of our objectives was to introduce as little perturbation as possible. This precluded our assessing preoperative $Sa_{O_2}$ and total volume of oxygen inspired after discontinuation of nitrous oxide; although these variables are very relevant to the likelihood of postoperative hypoxemia, they are not commonly measured in our hospital.

Arterial oxygen saturation of 90% ($Pa_{O_2} \cong 58$ mm Hg) has often been chosen to define hypoxemia (15,16), perhaps because the first objective signs of hypoxemia will usually have appeared at this saturation (17). But we believe that to some anesthesiologists, a $Pa_{O_2}$ of 58 mm Hg would be acceptable in healthy patients if it were to last only a minute or two. We, therefore, studied more profound hypoxemia as well. Our choice of 85% $Sa_{O_2}$ ($Pa_{O_2} \cong 50$ mm Hg) to define severe hypoxemia was somewhat arbitrary. Previous investigators (14) have safely induced 70% $Sa_{O_2}$ ($Pa_{O_2} \cong 37$ mm Hg) in healthy, conscious nonsmokers for approximately 20 min without ill effects. However, an extrapolated $Pa_{O_2}$ of 50 mm Hg in an unscreened patient population would be low enough to cause most anesthesiologists to intervene immediately. None of our severely hypoxemic patients developed postoperative complications related to hypoxemia.

There was a significant incidence of hypoxemia during postoperative transfer in our sample population. This population excluded patients with compromised pulmonary or cardiovascular function. Therefore, with the possible exception of the obese, our patients were those in whom hypoxemia would not be expected to occur. Of the variables considered—body weight, age, medical history, history of smoking, anesthesia duration, level of consciousness, and anesthetic agent—only significant obesity and a history of asthma could be shown to predict the development of postoperative hypoxemia. In patients whose $Sa_{O_2}$ did not fall below 85% the correlation between minimum $Sa_{O_2}$ and weight was highly significant statistically, but the correlation coefficient of 0.448 suggests that only 20% of the decrease in $Sa_{O_2}$ can be attributed to obesity. Thus the absence of obesity (or of a history of asthma) does not assure that a patient will not develop hypoxemia during postoperative transfer from the OR to the PAR.

There are several possible causes of postoperative hypoxemia. The dilution of alveolar gases by the efflux of $N_2O$ at the termination of anesthesia may play a role. This has led to the recommendation that patients be allowed to breathe 100% oxygen for at least 5 min after the discontinuation of $N_2O$ (16). But even after this has been done, a patient's alveolar–arterial oxygen tension gradient ($A\text{–}aD_{O_2}$) may be abnormal. Microatelectasis resulting in a ventilation/perfusion imbalance (6) or in a true shunt (18) is one source of this abnormal gradient. The effects of microatelectasis are exacerbated by any diminution of pulmonary hypoxic vasoconstriction by residual anesthetic gases. However, we found no statistically significant difference in postoperative hypoxemia between intravenous and inhalational agents. We did find a correlation between obesity and hypoxemia; obesity is known to increase the likelihood of the development of atelectasis (19).

A second possible source of abnormal $A\text{–}aD_{O_2}$ is the decrease during surgery of FRC below closing capacity (CC) (20), resulting in increased ventilation/perfusion imbalance. Because CC increases with age, one might expect a relation between age and incidence of postoperative hypoxemia, but we did not find one. Patients with symptomatic obstructive airway disease also have elevated CC (21), and the incidence of postoperative pulmonary complications in these patients has been reported to be high (22). It was remarkable, however, that in our sample, asymptomatic patients with a history of very mild asthma should distinguish themselves in this way from the general postoperative population. This finding supports the opinion of Levison et al. (23) that asthma is never completely cured, even in patients who have been asymptomatic for some time.

Although $Sa_{O_2}$ in all our patients was 97% or higher during the period of spontaneous respiration of 100% oxygen just prior to transfer, 11 patients became severely hypoxemic during transfer. In nine of these, $Sa_{O_2}$ quickly rose to and remained above 90% when supplemental oxygen was provided. In the other two, respiration was momentarily assisted, after which their $Sa_{O_2}$ also remained above 90%. Because all 11 patients began transfer with $Sa_{O_2}$ 97% or higher and all returned to normoxia without more than momentary ventilatory assistance when supplemental oxygen was supplied, it is reasonable to suppose that the automatic provision of supplemental oxygen throughout transfer would have prevented hypoxemia in all our patients.

In summary, we determined the incidence of postoperative hypoxemia during transfer to the recovery room in 95 healthy patients. A surprisingly high percentage of these patients did in fact become hypoxemic. It would be logical to assume, but we have not shown, that more severe hypoxemia would be found in patients undergoing more extensive surgery and in those with preexisting pulmonary disease. Because our data suggest that no single factor can explain postoperative hypoxemia, and because supplemental oxygen is innocuous under most circumstances (24), we conclude that the conservative and safe course is to provide supplemental oxygen during postoperative transfer as well as in the PAR to all patients who have had a general anesthetic.

We thank the anesthesiology staff of Magee-Women's Hospital for their cooperation, Dr. Ceferino Sinchioco for computer assistance, Ms. Lisa Cohn for editorial assistance, and Ms. Marjorie Faller for secretarial assistance.

## References

1. Nunn JF. Factors influencing the arterial oxygen tension during halothane anesthesia with spontaneous respiration. Br J Anaesth 1964;36:327–41.
2. Marshall BE, Wyche MQ. Hypoxemia during and after anesthesia. Anesthesiology 1972;37:178–209.
3. Craig DB. Postoperative recovery of pulmonary function. Anesth Analg 1981;60:46–52.
4. Ernsting J. The effect of brief profound hypoxia upon the arterial and venous oxygen tensions in man. J Physiol 1963;169:292–311.
5. Davidson MB. Diabetes mellitus: diagnosis and treatment. New York: Wiley, 1981:52.
6. Nunn JF, Payne P. Hypoxaemia after general anesthesia. Lancet 1962;2:631–2.
7. Harte PJ, Courtney DR, O'Sullivan EG, Brady MP. Duration of anesthesia and post-operative hypoxaemia. Ir J Med Sci 1982;151:169–74.
8. Ali J, Khan TA. The comparative effects of muscle transection and median and upper abdominal incisions on postoperative pulmonary function. Surg Gynecol Obstet 1979;148:863–6.
9. Kitamura H, Sawa T, Kezono E. Postoperative hypoxemia: the contribution of age to the maldistribution of ventilation. Anesthesiology 1972;36:244–52.
10. Vaughan RW, Engelbirdt RD, Wise L. Postoperative hypoxemia in obese patients. Ann Surg 1974;180:877–82.
11. Spence AA, Alexander JI. Mechanisms of post-operative hypoxaemia. Proc R Soc Med 1971;65:12–4.
12. Sheffer L, Steffenson MC, Birch AA. Nitrous oxide diffusion hypoxia in patients breathing spontaneously. Anesthesiology 1972;37:436–9.
13. Virtue RW, Myers D, Aldrete JA. Postanesthetic administration of doxepram hydrochloride and/or oxygen at an altitude of one mile. Anesth Analg 1972;51:1–5.
14. Yelderman MF, New W. Evaluation of pulse oximetry. Anesthesiology 1983;59:349–52.
15. Duncan D, Rose D, Bloom C, Hasse C, Poidmore S, Carlson R. Hypoxemia during outpatient general anesthesia. J Oral Maxillofac Surg 1982;40:421–3.
16. Frumin MJ, Edelist G. Diffusion anoxia: critical reappraisal. Anesthesiology 1969;31:243–9.
17. Cotes JE. Lung function: assessment and application in medicine, 4th ed. Oxford: Blackwell, 1979:468–70.
18. Diament ML, Palmer KNV. Venous arterial pulmonary shunting as the principal cause of post-operative hypoxaemia. Lancet 1967;1:15–7.
19. Anonymous. Post-operative atelectasis. Lancet 1977;2:965–6.
20. Alexander JI, Spence AA, Parikh RK, Stuart B. The role of airway closure in post-operative hypoxaemia. Br J Anaesth 1973;5:34–40.
21. Beeson PB, McDermott W, Wyngaarden JB. Cecil: textbook of medicine. Philadelphia: W.B. Saunders, 1979:953.
22. Latimer RG, Dickman M, Day CW, Gunn ML, Schmidt C. Ventilatory patterns and pulmonary complications after upper abdominal surgery determined by pre-operative and post-operative computerized spirometry and blood gas analysis. Am J Surg 1971;122:622–32.
23. Levison H, Collins-Williams C, Bryan AC, Reilly BJ, Orange RP. Asthma. Current concepts. Pediatr Clin North Am 1974;21:951–65.
24. Winter PM, Smith G. The toxicity of oxygen. A symposium review. Anesthesiology 1972;37:210–41.

ANESTH ANALG
1985;64:1113–6

# Intracranial Pressure after Atracurium in Neurosurgical Patients

Michael D. Minton, MD, Joseph A. Stirt, MD, Robert F. Bedford, MD, and Charles Haworth, MD

MINTON MD, STIRT JA, BEDFORD RF, HAWORTH C. Intracranial pressure after atracurium in neurosurgical patients. Anesth Analg 1985;64:1113–6.

*In order to investigate the usefulness of atracurium for neurosurgical anesthesia, we studied its impact on intracranial pressure (subarachnoid bolt) mean arterial pressure (radial artery catheter) and cerebral perfusion pressure (mean arterial pressure-intracranial pressure) in 20 patients undergoing elective craniotomy for brain tumor excision. General anesthesia was induced with thiopental, 4 mg/kg intravenously, and maintained with 70 percent nitrous oxide in oxygen. Ventilation was controlled by face mask, with end-tidal* $CO_2$ *held constant. Once intracranial pressure and mean arterial pressure had stabilized, the response to atracurium, 0.5 mg/kg intravenously, was continuously recorded for 5 min in 10 patients. An additional 10 patients received no atracurium and served as matched controls. Thiopental caused reductions in ICP in both groups of patients. Comparing the responses of the patients who received atracurium with those who did not, we found that atracurium had no significant effect on intracranial pressure, mean arterial pressure or cerebral perfusion pressure. Based on these data we conclude that atracurium appears to be preferable to the other available neuromuscular blocking agents that have been evaluated for neurosurgical anesthesia.*

Key Words: ANESTHESIA—neurosurgical. NEUROMUSCULAR RELAXANTS—atracurium. BRAIN—intracranial pressure.

The safe use of muscle relaxants in neurosurgical patients with reduced intracranial compliance requires that these agents have minimal impact on both hemodynamics and intracranial pressure (ICP). The cardiovascular stability associated with atracurium (1) suggests potential for use in neurosurgical anesthesia, although its effects on ICP have not been examined to date. For this reason we undertook an investigation of the effects of atracurium on ICP in patients with brain tumors.

## Methods

The study protocol was approved by the institution's Human Investigation Committee, and informed consent was obtained. The subjects were ten consecutive unpremedicated patients scheduled for elective craniotomy and tumor resection. Patients ranged in age from 27 to 70 yr and were free of significant concurrent cardiopulmonary disease. Preoperative computerized tomograms had revealed supratentorial tumors greater than 3 cm diameter in all patients. Seven patients had significant cerebral edema, and eight exhibited a shift of midline structures (Table 1).

An additional ten consecutive patients scheduled for elective craniotomy and tumor resection formed a control group not receiving atracurium. These patients ranged in age from 35 to 67 yr, and almost all had significant cerebral edema and a shift of midline structures (Table 2). A majority of patients in both groups received preoperative anticonvulsants and steroids.

A subarachnoid pressure screw, 20-gauge radial arterial catheter, and peripheral venous cannulae were placed with the patients under local anesthesia. All pressures were continuously transduced (Bentley Model 800 transducer) and recorded (Gould Model 440 polygraph) with the zero reference point at the external auditory meatus. Patency and function of the subarachnoid screw were assessed by observation of the respiratory and cardiac oscillations in the intracranial pressure waveform. After a stable period of arterial and intracranial pressures was observed, the intracranial volume–pressure relationship (VPR) was measured by injection of 1 ml of sterile saline through the pressure screw. With patients in the supine 15°

---

Presented in part at the 59th Congress of The International Anesthesia Research Society, Houston, Texas, March 1985.

Received from the Departments of Anesthesiology and Neurological Surgery, University of Virginia Medical Center, Charlottesville, Virginia. Accepted for publication June 7, 1985.

Address correspondence to Dr. Bedford, Department of Anesthesiology, Box 238, University of Virginia Medical Center, Charlottesville, VA 22908.

© 1985 by the International Anesthesia Research Society

Table 1. Age, CT Characteristics, and Intracranial Compliance in 10 Patients Subsequently Receiving Atracurium 0.5 mg/kg IV

| Patient number | Age (yr) | Tumor diameter (cm) | Cerebral edema[a] | Midline shift (mm) | ΔICP/ml (mm Hg) |
|---|---|---|---|---|---|
| 1 | 69 | 3 | 2 | 5 | 1 |
| 2 | 46 | 5 | 0 | 0 | 0 |
| 3 | 52 | 5.5 | 1 | 15 | 1 |
| 4 | 57 | 6 | 1 | 10 | 3 |
| 5 | 70 | 5 | 2 | 5 | 0 |
| 6 | 62 | 3 | 0 | 0 | 0 |
| 7 | 67 | 4 | 3 | 5 | 3 |
| 8 | 27 | 4.5 | 2 | 5 | 5 |
| 9 | 54 | 3 | 2 | 0 | 5 |
| 10 | 62 | 6 | 2 | 17 | 4 |

[a] 0, no edema; 3, edema throughout ipsilateral hemisphere.

Table 2. Age, CT Characteristics, and Intracranial Compliance in 10 Control Patients

| Patient number | Age (yr) | Tumor diameter (cm) | Cerebral edema[a] | Midline shift (mm) | ΔICP/ml (mm Hg) |
|---|---|---|---|---|---|
| 1 | 54 | 2 | 3 | 5 | 5 |
| 2 | 67 | 4 | 2 | 0 | 4 |
| 3 | 57 | 3 | 3 | 12 | 5 |
| 4 | 65 | 3 | 2 | 12 | 6 |
| 5 | 35 | 6 | 2 | 15 | 4 |
| 6 | 67 | 5 | 3 | 10 | 3 |
| 7 | 59 | 3 | 2 | 5 | 2 |
| 8 | 56 | 5 | 2 | 5 | 8 |
| 9 | 47 | 7 | 1 | 20 | 4 |
| 10 | 63 | 5 | 2 | 15 | 4 |

[a] 0, no edema; 3, edema throughout ipsilateral hemisphere.

head-up position, anesthesia was induced with thiopental, 4 mg/kg intravenously, and maintained with 70% nitrous oxide in oxygen. Additional increments of thiopental were administered if necessary to obtund lash reflex or allow prompt control of ventilation by facemask. Constancy of controlled ventilation was monitored with breath-to-breath end-tidal $CO_2$ measurement (Hewlett Packard H-P 47210-A Capnometer) and verified by arterial blood gas determinations at 1 and 4 min after induction of anesthesia.

When ICP and arterial pressures had stabilized after induction of anesthesia, atracurium, 0.5 mg/kg intravenously, was given over 5 sec to the first 10 patients, and constant controlled ventilation was continued for 5 min after atracurium injection. In the group of 10 patients who did not receive atracurium, mask ventilation with $N_2O$ 70% in $O_2$ was continued for 5 min after stabilization of ICP and arterial pressures after thiopental.

Recorded values for ICP and calculated values for mean arterial pressure (MAP = diastolic pressure + ⅓ pulse pressure) and cerebral perfusion pressure (CPP = MAP − ICP) were tabulated every minute after induction of anesthesia and were compared using one-way analysis of variance with both the awake control values and the values measured immediately after induction of anesthesia. Arterial $CO_2$ tensions determined just after induction of anesthesia were compared with those obtained 3 min later using Student's *t*-test for paired data. $P < 0.05$ was considered significant.

## Results

Radiographic characteristics and results of VPR measurements are shown in Tables 1 and 2. Eight patients receiving atracurium and all patients in the control group had evidence to suggest compromised intracranial compliance by either computed tomography scan (effacement of lateral ventricles, 5-mm shift of midline structures) or by VPR measurements greater than 3 mm Hg/ml. Study results are displayed in Tables 3 and 4. Thiopental, 4 mg/kg, caused significant reductions in ICP in both groups and a brief but significant decrease in MAP in the control group. Thereafter both MAP and CPP were unchanged statistically

Table 3. Intracranial Pressure, Mean Arterial Pressure, Cerebral Perfusion Pressure, and Arterial $P_{CO_2}$ in 10 Patients before and during Thiopental–$N_2O$ Anesthesia with Atracurium

| | Awake control | After thiopental | Time (min) after atracurium administration | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 0 | 1 | 2 | 3 | 4 | 5 |
| ICP (mm Hg) | 12.9 ± 1.2 | 10.7 ± 1.4[a] | 14.3 ± 1.9 | 15.6 ± 1.7 | 16.0 ± 1.8 | 17.3 ± 2.2 | 17.2 ± 2.5 | 18.3 ± 3.0 |
| MAP (mm Hg) | 94.8 ± 4.2 | 90.4 ± 7.6 | 90.1 ± 7.6 | 84.3 ± 7.4 | 81.6 ± 7.2 | 78.4 ± 7.5 | 82.9 ± 8.8 | 85.8 ± 8.3 |
| CPP (mm Hg) | 81.9 ± 4.2 | 79.7 ± 6.3 | 75.6 ± 8.3 | 68.8 ± 7.9 | 65.6 ± 8.0 | 61.1 ± 8.0 | 66.2 ± 8.5 | 67.6 ± 7.4 |
| $Pa_{CO_2}$ (mm Hg) | | | 38 ± 2 | | | 39 ± 2 | | |

All values are mean ± SEM.

[a] $P < 0.05$ compared to awake control.

Table 4. Intracranial Pressure, Mean Arterial Pressure, Cerebral Perfusion Pressure, and Arterial $P_{CO_2}$ before and during Thiopental–$N_2O$ Anesthesia without Atracurium

| | Awake control | After thiopental | Time (min) after stable conditions | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 0 | 1 | 2 | 3 | 4 | 5 |
| ICP (mm Hg) | 15.5 ± 0.8 | 8.1 ± 1.2[a] | 10.0 ± 1.1[a] | 13.5 ± 1.2 | 14.7 ± 1.2 | 16.3 ± 1.4 | 17.7 ± 1.6 | 17.8 ± 2.0 |
| MAP (mm Hg) | 94.3 ± 2.8 | 80.4 ± 2.9[a] | 87.8 ± 2.9 | 91.2 ± 2.9 | 93.0 ± 4.7 | 91.3 ± 4.2 | 97.0 ± 4.3 | 97.5 ± 4.1 |
| CPP (mm Hg) | 79.0 ± 3.5 | 72.5 ± 2.4 | 77.8 ± 2.6 | 78.8 ± 2.5 | 78.3 ± 4.0 | 75.0 ± 3.3 | 78.7 ± 3.3 | 79.7 ± 3.4 |
| $Pa_{CO_2}$ | | | 36.9 ± 1.8 | | | 37.8 ± 1.8 | | |

All values are mean ± SEM.

[a] $P < 0.05$ compared to awake control.

from awake control levels throughout the study period. No statistically significant changes in ICP occurred after atracurium, 0.5 mg/kg intravenously. Although CPP tended to be lower in the group of patients who received atracurium, at no time did this achieve statistical significance compared to the control patients. Furthermore, no instances of marked increase in ICP or marked decrease in MAP or CPP were noted in any of the patients. Arterial blood gas tensions did not change during the study period, verifying constancy of controlled ventilation.

## Discussion

To date, the effects of neuromuscular blocking agents on ICP in humans have not been well defined, and both hemodynamic and intracranial effects must be considered in the proper selection of relaxants. Administration of succinylcholine has been associated with increases in ICP (2–6) or lumbar cerebrospinal fluid pressure (7,8), but some studies have shown it to have no effect (9–11). Variability in species, patient population, and study design have made interpretation and comparison of studies difficult, and the use of succinylcholine in neurosurgical anesthesia has been the subject of varied recommendations (5,12–14) and spirited debate (12,13).

Although previous investigations of pancuronium (2,3) and gallamine (9) have not demonstrated an adverse impact on ICP, the potential for tachycardia and hypertension with both of these agents (15–17) suggests the need for caution when used in patients with intracranial vascular pathology or severely impaired autoregulation. *d*-Tubocurarine has been associated with increases in ICP in both animals (11) and humans (18), possibly due to histamine-induced cerebrovascular vasodilation (18,19). Intubating doses of curare may lead to hypotension (18), which, in concert with increases in ICP, may seriously compromise cerebral perfusion. Previous investigations of atracurium, however, have demonstrated minimal hemodynamic effects (1) and little histamine release (20). Our present work has shown that it possesses no effect on ICP in patients with intracranial tumors.

In our study, administration of atracurium at conventional intubation doses was superimposed upon a baseline of 70% nitrous oxide in oxygen anesthesia after thiopental induction. Noxious stimuli known to cause increases in ICP, either with (21,22) or without (22) hemodynamic changes, were avoided during the study period. Constant controlled ventilation by face mask was monitored by breath-to-breath end-tidal $CO_2$ analysis and normocarbia was verified by multiple arterial blood gas determinations. Direct measurement of intracranial pressure was obtained through a properly functioning subarachnoid pressure screw.

Although there was no significant change in ICP after atracurium, we observed a gradual increase of approximately 4 mm Hg in intracranial pressure during the study period after atracurium administration.

An identical trend was observed in the control group, and thus we believe there was no intrinsic effect of atracurium on ICP. Similar findings have been shown previously with nitrous oxide anesthesia (23–27) that were attributed to cerebral vasodilation and increased intracranial blood volume (24). Though this increase did not assume statistical significance, it may be of some clinical importance, and probably could have been prevented by institution of concomitant hyperventilation (24,28) or administration of additional barbiturate (26).

In conclusion, these data show that atracurium, 0.5 mg/kg intravenously, affords both the hemodynamic stability and absence of effect on ICP necessary for safe use in patients with intracranial masses and reduced intracranial compliance.

## References

1. Basta SJ, Ali HH, Savarese JJ, Sunder N, Gionfriddo M, Cloutier G, Lineberry C, Cato AE. Clinical pharmacology of atracurium besylate (BW33A): a new non-depolarizing muscle relaxant. Anesth Analg 1982;61:723–9.
2. McLeskey CH, Cullen BF, Kennedy RD, Galindo A. Control of cerebral perfusion pressure during induction of anesthesia in high-risk neurosurgical patients. Anesth Analg 1974;53:985–92.
3. Lewelt W, Moszynski K. Kozniewska H. Effect of depolarizing and non-depolarizing muscle relaxants and intubation on the ventricular fluid pressure. In: Beks JWF, Bosch DA, Brock M, eds. Intracranial pressure III. New York: Springer Verlag, 1976;215–8.
4. Moszynski K. Dynamic changes in cerebrospinal fluid pressure during neurosurgical operations. Acta Neurochir 1976;34:285–6.
5. Marsh ML, Dunlop BJ, Shapiro HM, Gagnon RL, Rockoff MA. Succinylcholine-intracranial pressure effects in neurosurgical patients. Anesth Analg 1980;59:550–1.
6. Cottrell JE, Hartung J, Griffin V, Shwiry B. Intracranial and hemodynamic changes after succinylcholine administration in cats. Anesth Analg 1983;62:1006–9.
7. Halldin M, Wahlin A. Effect of succinylcholine on the intraspinal fluid pressure. Acta Anaesth Scand 1959;38:155–61.
8. Marx GF, Andrews IC, Orkin LR. Cerebrospinal fluid pressures during halothane anesthesia. Can Anaestha Soc J 1962;9:239–45.
9. Weiss M, Wertman N, Apuzzo M, Heiden J, Kurze T. Influence of myoneural blockers on intracranial dynamics. Bull Los Angeles Neuological Soc 1977;42:1–7.
10. Bormann BE, Smith RB, Bunegin L, Albin MS. Does succinylcholine raise intracranial pressure? Anesthesiology 1980;53:S262.
11. Paul WL, Bishko JR, Woodham B. Succinycholine, *d*-tubocurarine, dimethyl-tubocurarine, and intracranial pressure in dogs. Anesth Analg 1981;60:269.
12. Lam AM, Gelb AW. Succinylcholine and intracranial pressure—a cause for "pause." Anesth Analg 1984;63:620.
13. Cottrell JE, Hartung J, Giffen JP, Shwiry B. Succinylcholine and intracranial pressure—a cause for "pause." Anesth Analg 1984;63:620–2.
14. Shapiro HM. Neurosurgical anesthesia and intracranial hypertension. In: Miller RD, ed. Anesthesia. New York: Churchill Livingston, 1981:1079–132.
15. Stoelting RK. Hemodynamic effects of pancuronium and *d*-tubocurarine in anesthetized patients. Anesthesiology 1972;36:612–5.
16. Smith NT, Whitcher CE. Hemodynamic effects of gallamine and tubocurarine administered during halothane anesthesia. JAMA 1967;199:704–8.
17. Thomas ET. The effect of gallamine triethodide on blood pressure. Anaesthesia 1963;18:316–23.
18. Tarkkanen L, Laitinen L, Johansson G. Effects of *d*-tubocurarine on intracranial pressure and thalamic electrical impedence. Anesthesiology 1974;40:247–51.
19. Savarese J. Histamine, *d*-tubocurarine and CSF pressure. Anesthesiology 1975;42:369.
20. Basta SJ, Savarese JS, Ali HH, Moss J, Gionfriddo M. Histamine-releasing potencies of atracurium, dimethyl tubocurarine, and tubocurarine. Br J Anesth 1983;55:105S–6S.
21. Burney R, Winn R. Increased cerebrospinal fluid pressure during laryngoscopy and intubation for induction of anesthesia. Anesth Analg 1975;54:687–90.
22. Shapiro H, Wyte S, Harris A, Galindo A. Acute intraoperative intracranial hypertension in neurosurgical patients: mechanical and pharmacologic factors. Anesthesiology 1972;37:399–405.
23. Laitinen LV, Johansson G, Tarkkanen L. The effect of nitrous oxide on cerebral impedance and cerebral blood flow. Br J Anaesth 1967;39:781–5.
24. Henrickson H, Jorgenson P. The effect of nitrous oxide on intracranial pressure in patients with intracranial disorders. Br J Anaesth 1973;45:486–91.
25. Greenbaum R, Cooper R, Hulme A, Mackintosh IP. The effect of induction of anesthesia on intracranial pressure. In: Arias A, ed. Recent progress in anesthesiology and resuscitation, International Congress Series No. 347. Amsterdam: Excerpta Medica, 1975;794–801.
26. Phirman JR, Shapiro HM. Modification of nitrous oxide-induced intracranial hypertension by prior induction of anesthesia. Anesthesiology 1977:46;150–1.
27. Moss E, McDowall DG. ICP increases with 50% nitrous oxide in oxygen in severe head injuries during controlled ventilation. Br J Anaesth 1979;51:757–60.
28. Misfeldt BB, Jorgenson PB, Rishoj M. The effect of nitrous oxide and halothane upon the intracranial pressure in hypocapnic patients with intracranial disorders. Br J Anaesth 1974;46:853–8.

ANESTH ANALG
1985;64:1117–25

## Review Article

# Supplemental Medication for Ambulatory Procedures under Regional Anesthesia

Beverly K. Philip, MD

Increasing numbers of ambulatory surgical procedures are being performed in hospitals, surgery centers, and doctor's offices; many of these procedures can be advantageously performed under regional anesthesia. This review article will discuss supplemental medication for the adult patient having regional anesthesia for ambulatory surgery. The introduction will address the role of pharmacologic supplementation, the characteristics of drugs appropriate for ambulatory patients, and the use of verbal reassurance as sedation. This will be followed by a review of the pharmacology of selected suitable drugs, including dosage, duration of action, advantages, and adverse effects.

Supplemental medication for ambulatory regional anesthesia serves two major functions. One is to provide chemically induced tranquility and relaxation during the surgical procedure. Supplemental sedation can thereby improve acceptance of regional techniques, particularly when a patient would rather not be fully awake in the operating room (76). The second function of supplemental medication is to provide additional analgesia that is useful even with a successful regional block. Patients may experience sensations of pressure, movement, or visceral traction that can be reduced with concomitantly administered analgesics. Supplemental analgesics can also ease the discomfort of having to lie still on a hard operating table. Supplemental ataractics and analgesics can greatly increase the ambulatory patient's satisfaction with regional anesthetic techniques.

Because the ambulatory patient will be discharged within a few hours of operation, there are special constraints placed on the choice of supplemental medications. These drugs should have an appropriately short onset and duration of action, few side effects, and a minimal likelihood of adverse reactions developing after discharge. Appropriate doses must be chosen; the recovery time from local anesthesia with excessive sedation can be longer than from general anesthesia (41,55). Long-acting amnesia is also undesirable because the ambulatory patient must remember the postanesthetic and postsurgical discharge instructions (in addition to those given in writing). Supplemental drugs for the ambulatory regional anesthesia patient should be carefully selected to achieve desired results with minimal side effects and rapid recovery.

It should be emphasized that verbal reassurance is an effective supplementation for ambulatory regional procedures. Many patients remain concerned during surgery about the anesthesia, about the operation, and about possible complications. These fears are best combatted by providing information and emotional support throughout the procedure so that the patient remains calm. Need for supplemental medications will thereby decrease (33). The patient can also be helped to remain calm by limiting intraoperative noise due to instruments and loud conversation; distraction with music through headphones is a useful adjunct.

## Pharmacology of Suitable Drugs

Supplemental medication for ambulatory regional anesthesia is best given intravenously. Drugs should be administered in small, incremental doses and the effect titrated carefully. Intraoperative supplementation can also be given as a continuous infusion, which may result in lower total drug doses and fewer side

---

Received from the Department of Anesthesia, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. Accepted for publication June 3, 1985.

Address correspondence to Dr. Philip, Department of Anesthesia, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115.

© 1985 by the International Anesthesia Research Society

effects (114). Supplemental sedation and analgesia may also be administered by inhalation when appropriate. Table 1 provides a summary of approximate dosages for selected drugs.

Table 1. Use of Selected Drugs for Supplemental Medication

| Class | Drug | Suggested dose | References |
|---|---|---|---|
| Ataractics | Diazepam | 0.05–0.15 mg/kg | 5,52 |
| | Midazolam | 0.03–0.15 mg/kg | 20,28 |
| | Droperidol | 5–17 μg/kg | 68,98,117 |
| Analgesics | Fentanyl | 1–3 μg/kg | 18,47,88 |
| | Alfentanil | 5–20 μg/kg | 100,105 |
| Inhalation analgesia | Enflurane | 0.5% | 1,66 |
| | Nitrous oxide | 30–50% | 32,40,108 |

## *Ataractics*

*Benzodiazepines.* Diazepam is the benzodiazepine most widely used for supplemental sedation (see Table 1). Sedation appears within 2–3 min of intravenous administration (6). Diazepam is rapidly cleared from plasma, with a distribution half-life of approximately 1 hr (59). However, the total dose of intravenous diazepam should be limited to avoid prolonged effects. Ataxia and dizziness sufficient to delay discharge are present in 8 and 16% of subjects, respectively, 1 hr after administration of 10 mg (16). After 20 mg, these causes of delayed discharge are present in 40 and 30% of subjects. Tests of coordination and reaction time are abnormal for 6 hr after 0.15 mg/kg of intravenous diazepam (64). To avoid oversedation of the ambulatory patient, diazepam should be used in 2.5-mg increments at intervals of no less than 3 min. Individual response is widely variable, and drug dosage must be reduced in the elderly (74).

After a period of early recovery, drowsiness and an increase in plasma concentration have been reported at 6–8 hr, probably due to enterohepatic recirculation (6). Also related to enterohepatic recirculation is an increase in serum concentration and drowsiness that occurs when fatty solid foods are consumed 3–7 hr after diazepam administration (66). Fatty food intake should be limited during the recovery of the ambulatory patient to avoid resedation, particularly when higher drug doses have been used.

Diazepam is biotransformed by hepatic metabolism. Its elimination half-life is 24–48 hr in adult subjects and is even longer in the elderly (60,74). Diazepam metabolites, notably desmethyldiazepam, are also pharmacologically active. After intravenous diazepam administration, plasma levels of desmethyldiazepam increase over 48 hr, and the elimination half-life of this metabolite is 51–120 hr (6,74). Diazepam should not be considered a drug with short duration of action, and ambulatory patients should be cautioned that they may feel tired for a day or more after diazepam administration.

To supplement regional anesthesia, some give diazepam until slurred speech and drooping eyelids occur. This has resulted in large doses, averaging 0.31 mg/kg for outpatient dental procedures (41) and 0.45 mg/kg for outpatient endoscopies (111). Korttila and Linnoila (64) studied the effect of 0.30 and 0.45 mg/kg diazepam on skills related to driving. Although Romberg tests are negative after 36 min, impairment of coordination and reactive skills persist until 10 hr. Tests of attention are minimally affected. Narcotics are often given in conjunction with diazepam to supplement sedation; this combination delays the return of normal function (63). Patients should be cautioned not to drive or operate dangerous machinery for at least 10 hr after sedation with high-dose diazepam and 24 hr after diazepam with long-acting narcotics.

The major drawbacks of diazepam administered intravenously for supplemental sedation are local pain and phlebitis. Because diazepam is insoluble in water, it is formulated in organic solvents including propylene glycol and ethyl alcohol (Valium, Roche Laboratories, Nutley, NJ). Three days after 0.3 mg/kg diazepam is injected intravenously into the dorsum of the hand, 100% of 8 patients develop phlebitis (42). When 5 mg diazepam is injected into the larger cephalic vein at the wrist, the incidence of sequelae is less: at 3 days, there is tenderness in 19% and thrombophlebitis in 17% of 47 patients (80). The incidence of venous sequelae after diazepam increases with time: 23% after 2–3 days and 39% after 7–10 days (46). Also, a faster rate of injection is associated with a higher incidence of immediate pain (66). Flushing the vein vigorously with saline may reduce subsequent thrombophlebitis.

Diazepam is available in an oil emulsion in Europe, as Diazemuls (Kabi-Vitrum, Sweden). This preparation has a lower reported incidence of immediate pain (1%)(101) as well as thrombophlebitis (6% after two weeks) (54). The Diazemuls formulation, while equally effective, is more expensive (68).

Diazepam is particularly useful with regional anesthesia because it increases the seizure threshold for local anesthetics (23). This should not, however, be construed as a reason to exceed the permissible dose of local anesthetic.

Diazepam should not be given to ambulatory patients without monitoring respiration. Doses of 0.14 mg/kg intravenously depress the ventilatory response to $CO_2$, increase the dead space to tidal volume ratio, and increase arterial $P_{CO_2}$ (12). These effects start within

1 min and last 25–30 min (45). Depression of ventilatory response correlates with drowsiness.

Clinical overdoses of diazepam may be given accidently; various antagonists have been tried. Naloxone, 0.4 mg (13), physostigmine, 1–2 mg (8,43), and aminophylline, 1 mg/kg (106), have all been used with inconsistent success and with significant side effects including nausea, vomiting, changes in blood pressure, and cardiac dysrhythmias. The routine use of any of the above drugs to antagonize diazepam effects in the ambulatory patient is not recommended. A specific benzodiazepine antagonist (RO 15-1788) is being developed that reverses both soporific and respiratory depressant effects, but its relative duration of action and side effects are still under investigation (25,70).

Diazepam is able to produce anterograde amnesia. A lack of recall after 5 or 10 mg intravenous diazepam develops in 50 and 90% of patients, respectively; amnesia is present at 1 min, peaks at 2–3 min, and persists approximately 30 min (27). The percentage of volunteers who develop anterograde amnesia is increased by a more rapid rate of diazepam injection (66). Retrograde amnesia after intravenous diazepam has been variably reported (15,22). Diazepam given intravenously may be used to produce brief amnesia in the ambulatory patient receiving regional anesthesia, for the insertion of the block or for the operative procedure. Although 10-mg intravenous bolus doses have been studied, the use of 2.5-mg increments is preferred in the ambulatory patient, to avoid oversedation. This may limit the amnesia obtained. It should also be emphasized that some patients become distressed when they cannot recall perioperative events (19), particularly those patients who choose regional anesthesia to remain aware of their surroundings. The potential for amnesia should be discussed with the patient in advance.

Lorazepam is a benzodiazepine that causes significant sedation and amnesia, but the duration of these effects is long (86), and its use is not recommended for supplementation of ambulatory regional anesthesia (26).

Midazolam is a new benzodiazepine that is twice as potent as diazepam (28) (see Table 1). Anterograde amnesia has been reported in 90–96% of patients after 5-mg intravenous midazolam; this effect is present at 2 min after injection and declines over the ensuing 20–40 min (20,29). Retrograde amnesia has not been demonstrated. Sedation and anxiolysis appear within 1–2 min after 5 mg (20), and marked sedation persists for at least the half-hour of observation. In other studies using a 5-mg dose, motor performance recovers in 34 min, and subjects are fully awake and walking unaided at 73 min (28,42). There is considerable variation in individual response. Midazolam plasma levels demonstrate a short half-life of 60–90 min, without evidence of enterohepatic recirculation and recurrence of drowsiness.

Midazolam has been compared to diazepam for supplementation of ambulatory regional anesthesia. Dixon et al. (24) gave a total of 0.10 mg/kg midazolam or 0.18 mg/kg diazepam to patients having spinal, epidural, and brachial plexus blocks. The degree of intraoperative sedation is similar after either sedative when these moderate doses are used. However, when residual sedation is evaluated after two hours' recovery, 80% of the patients who receive midazolam are awake. After the same period of recovery from diazepam, patients remain more sedated; only 67% are awake. Amnesic effectiveness under these conditions can also be compared (24). Fifty percent of patients who receive 0.10 mg/kg midazolam remember nothing of their operation, but only 18% of patients who receive 0.18 mg/kg diazepam are completely amnesic. Midazolam, rather than diazepam, does provide relatively more rapid recovery and more effective amnesia when used to supplement regional anesthesia for ambulatory dental (5) and endoscopic (99) procedures as well.

However, large doses of midazolam will result in prolonged effects. Three hours after sedation with 0.19 mg/kg midazolam, 50% of patients having had spinal anesthesia remain drowsy or asleep (76). To supplement ambulatory regional anesthesia, midazolam should be given in small 1–2-mg increments and time should be allowed for its effect to develop.

Midazolam is water-soluble, and venous irritation is minimal. Dundee et al. (28) report no pain on injection and no thrombophlebitis 2 weeks after 5 or 10 mg of midazolam. Microscopic examination of rat veins after midazolam administration shows no pathologic alteration (85). Considering its effective sedation, short duration of action, and minimal irritation of veins, midazolam holds great promise as supplemental medication for ambulatory procedures.

*Droperidol.* Droperidol has been used for many years as a supplement to surgical and diagnostic procedures. This butyrophenone derivative produces sedation and a sense of detachment. Amnesia is minimal (65). Droperidol does not significantly affect respiration (36) although wide individual variation of response occurs (91). When droperidol is administered with a narcotic, neuroleptanalgesia results. Overenthusiastic use of droperidol for sedation, alone and in neurolept combinations, generated many reports of complications including prolonged and excessive sedation, hypotension, extrapyramidal symptoms, and apprehension and anxiety despite apparent drowsiness (35,38,47,67,81). Doses given were 0.04–0.17 mg/kg in adults and 0.1–0.17 mg/kg in children (30). Patients sometimes become anxious, agitated, and confused to the extent that they cancel previously agreed-to elective surgery. The incidence of refusal was 4.7% in a series of 121 military patients for plastic surgery (10) and 0.7% in a series of 1438 private patients scheduled for sterilization or plastic surgery procedures (69). Such larger doses of droperidol should not be used for sedation of ambulatory patients.

In addition to producing unacceptable side effects, the duration of sedation is too long after doses of 0.04 mg/kg or more. Korttila and Linnoila (65) evaluated recovery and driving-related skills after intravenous injection of 5 mg of droperidol. Clinical recovery as determined by a negative Romberg sign is present after 25 min, but tiredness or drowsiness is still reported after 10 hr by 50% of the volunteers. Tests of coordination and attention remain significantly abnormal at the final 10-hr testing. The concurrent administration of fentanyl, 0.2 mg, does not affect the results of objective tests.

Droperidol, 2.5 mg/ml, is sold alone and in combination with fentanyl, 0.05 mg/ml, as Innovar (Janssen Pharmaceutica, New Brunswick, NJ). This neurolept combination is, in general, not appropriate for supplementation of ambulatory patients. The sedation caused by this relatively large dose of butyrophenone far outlasts the analgesic effect of the narcotic component.

Droperidol in lowered dosage is useful to supplement ambulatory procedures, for its sedative and particularly for its antiemetic properties (53,116) (see Table 1). Doses of 0.005–0.017 mg/kg (0.625–1.25 mg in adults) significantly reduce the incidence of postoperative vomiting in adults and children (62,95,113). Droperidol is effective by the intravenous or intramuscular route, particularly when given pre- or intraoperatively. Side effects such as excessive sedation, extrapyramidal symptoms, or anxiety are not seen at these doses. Droperidol may be given prophylactically to the patient with a history of previous postoperative vomiting (93), or to the patient whose procedure is associated with a high incidence of emesis, such as ocular (2,51,56,84) or gynecologic (18,78,82,88) surgery. Droperidol also significantly reduces emesis if given postoperatively at the onset of symptoms (72,113).

## *Analgesics*

*Fentanyl.* Fentanyl is a potent narcotic congener of meperidine. After intravenous administration, subjective response to fentanyl (3.2 μg/kg) begins within 2 min and lasts 45–60 min (75). Study of plasma fentanyl kinetics shows that termination of effect is due to redistribution into blood and peripheral tissues. The redistribution half-life of fentanyl is 13.4 min, and 98.6% of the injected dose is cleared from plasma in 60 min (75). These rapid early drug kinetics illustrate why fentanyl has become the most widely used narcotic to supplement ambulatory procedures (see Table 1). Increments of 25–50 μg fentanyl may be given intravenously to achieve desired analgesia, with an initial dose totalling 50–200 μg (1–3 μg/kg). Additional doses may be given in 30–60 min as clinically indicated. The elderly require reduced drug doses.

Although fentanyl is an appropriate narcotic for ambulatory procedures, its use is not without problems. Fentanyl causes marked respiratory depression. A dose of 1.3 μg/kg results in depression of $CO_2$ response slope comparable in magnitude and duration to that seen after 0.12 mg/kg morphine (94), with both responses remaining below 80% of control for 4 hr. There is also evidence of a recurrence of respiratory depression, accompanied by decreases in $Pa_{O_2}$ and pH and an increase in $Pa_{CO_2}$ (7,108). Respiratory depression occurs first at 30–60 min and again thereafter, with wide individual variation. These delayed effects may be due to secretion of fentanyl into gastric juice and reabsorption from the small intestine (107), or due to the return of unchanged active fentanyl from peripheral compartments such as muscle, when increased patient activity causes increased blood flow (75). The delayed hepatic metabolism and slow elimination half-life of fentanyl, 219 min, may reflect this drug return. The clinician should be aware that somnolence, respiratory depression requiring ventilatory support, and respiratory arrest have occurred 0.5–4 hr after apparent recovery from fentanyl administration (3). The addition of droperidol, given as Innovar, does not alter the respiratory depression caused by fentanyl (7). Rigidity after fentanyl (14,100,103) has not been reported in the awake sedated ambulatory patient.

Naloxone has been used to reverse narcotic side effects, primarily respiratory depression. Naloxone, however, has sequelae of its own. Unless carefully titrated, it can eliminate the analgesia. Hypertension, pulmonary edema, ventricular arrhythmias, and cardiac arrest in healthy patients have been reported after 0.1–0.4 mg naloxone (4,92,109). The routine "prophylactic" use of naloxone after fentanyl supplementation cannot be recommended.

Continuous infusion of fentanyl rather than intermittent bolus administration has been used for ambulatory patients (114). After a 100-μg loading dose, fentanyl is administered as $0.1\ \mu g \cdot kg^{-1} \cdot min^{-1}$ of a 2 μg/ml infusion solution rather than in 50-μg increments. A 45% decrease in the total dose results: 233

μg for a 23-min procedure. With the lower dose, intraoperative motor and cardiovascular side effects are less frequent and time to awakening decreases 62%. Excessive postoperative sedation decreases from 48 to 4%, and discharge times decrease by 29%. If an ongoing need for fentanyl supplementation is anticipated, the continuous infusion technique may be advantageous.

*Other opioids.* New narcotics have been synthesized in an attempt to achieve analgesia with fewer side effects. The agonist–antagonists butorphanol and nalbuphine are two such drugs with potential use for ambulatory supplementation. Butorphanol is approximately five times as potent as morphine, while nalbuphine is considered to be equipotent with morphine. These narcotics cause limited respiratory depression; with continued drug administration, only minimal increases occur after the equivalent of 10 mg of morphine. Butorphanol has a subjectively pleasant, slightly sedative effect. Onset of action for either drug is within 2 min after intravenous administration. Unfortunately, their duration of action is long, similar to morphine. Fine and Finestone (37) used moderately large doses of these drugs (butorphanol, 0.06 mg/kg, and nalbuphine, 0.3 mg/kg) with thiopental and nitrous oxide for cystoscopy, and they found the incidence of side effects and duration of recovery greater than with fentanyl (0.003 mg/kg). The place for reduced doses of these agonist–antagonist narcotics to supplement ambulatory procedures has not been evaluated.

Some longer-acting opioid analgesics have been popular supplements in specific institutions, usually as a holdover from inpatient use. Morphine and meperidine are two such drugs. The use of longer-acting opioids results in a longer duration of sedation and of other side effects such as nausea and dizziness. Meperidine in particular is not recommended for outpatient administration. Intramuscular meperidine is associated with syncope after standing up, and tests of coordination and reaction time remain abnormal 12 hr after the administration of 75 mg (63). The use of such longer-acting opioid analgesics should be avoided as supplementation for the ambulatory patient (79).

The needs of outpatient anesthesia have prompted the search for new short-acting narcotic analgesics. Alfentanil (57,77,83) is a fentanyl analog with approximately one-quarter the potency and one-third the duration of action of the older drug (see Table 1). The pharmacokinetic characteristics of alfentanil include a rapid redistribution half-life, 11.6 min, and an elimination half-life of 94 min (9), which is considerably shorter than that of fentanyl (219 min (75)). Termination of alfentanil's effect is primarily dependent on hepatic metabolism rather than on redistribution, and prolongation of action after large or repeated doses should not occur (49,104). No secondary increases in alfentanil plasma concentration have been reported. Recovery after ambulatory procedures has consistently been rapid if appropriate doses are used (87,96,102).

The pharmacokinetics of alfentanil suggest that it may best be used by continuous infusion for the supplementation of ambulatory regional anesthesia. Patients have been given a loading dose of 250–500 μg alfentanil, followed by 40–70 μg/min of a 10 μg/ml solution (16). Use of an infusion rather than intermittent 250-μg boluses results in a 38% decrease in total dose. Times to awakening, orientation, and ambulation are also decreased. Continuous infusion of alfentanil for postoperative analgesia has also been successful, with a mean rate of use of 8.1 ± 1.7 μg/min (58).

## *Inhalation Analgesia*

Anesthetic gases and vapors administered at subanesthetic concentrations provide analgesia and sedation. These effects can be used to supplement regional anesthesia for ambulatory procedures. Advantages of inhalation over intravenous analgesia are related to the mode of drug administration: ventilation through the lung. These advantages include rapid reversibility and easier maintenance of a constant blood concentration and, therefore, constant anesthetic effect (34,89). A disadvantage is the need to administer the gas or vapor through a tight-fitting mask or mouthpiece, to provide adequate drug intake and to avoid contamination of operating room air. Inhalation analgesia is particularly useful for minor surgery on closed space infections, which are difficult to block with local anesthetic (39). Adult, pediatric (11,44), and mentally retarded (50) patients are all satisfactory candidates.

Most inhalation anesthetic agents have been used for analgesia. Methoxyflurane is well accepted by patients and is effective for inhalation analgesia when given intermittently at concentrations of 0.2–0.5% (1.2–3.1 MAC) (17). However, methoxyflurane is metabolized in part to inorganic fluoride, and serum fluoride levels above 50 μM/L have been associated with polyuric renal failure. This level has been reached in patients self-administering methoxyflurane for obstetric pain relief (73). The use of methoxyflurane analgesia for ambulatory patients is not recommended due to the possibility of renal damage.

Isoflurane could also be used for subanesthetic inhalation analgesia. Potential advantages of isoflurane include rapid induction and emergence, due to the agent's low blood/gas solubility, and less possibility for renal or hepatic toxicity, due to minimal metabolism. However, its use for inhalation analgesia is limited in practice because isoflurane has a pungent odor and can cause respiratory tract irritation, which reduces acceptance of the drug (112).

Halothane is well tolerated and has been employed for inhalation analgesia particularly for dental procedures (98). However, the use of halothane has been largely supplanted by enflurane, because the incidence of cardiac dysrhythmias during oral surgery is markedly reduced from 34.2 to 2.7% when the latter agent is used (115). Local anesthetic blockade does decrease the incidence of arrhythmias associated with dental surgery and halothane (90), but the potential for halothane-related hepatotoxicity remains a problem.

Subanesthetic concentrations of enflurane are effective and are used to provide supplemental analgesia for ambulatory procedures (see Table 1). Psychomotor testing during enflurane inhalation show that digit memory, audiovisual reaction time, and manual dexterity are impaired at end-tidal concentrations greater than 0.09 MAC (0.2% inspired) (21). At 0.24 MAC enflurane (0.53% inspired), sufficient drowsiness sometimes develops to preclude completing the tests. Dose-related amnesia is seen also. Similar concentrations, approximately 0.5% inspired enflurane or 40% inspired nitrous oxide, have been reported to achieve maximal analgesia without loss of consciousness in obstetric patients (1). Satisfactory pain relief is reported by 89 and 76% of the parturients for the two agents, respectively, and complete amnesia (of delivery) develops in 7 and 10% of patients. The difference between the agents is not significant.

Nitrous oxide has achieved widespread popularity particularly as an adjunct to dental regional anesthesia (see Table 1). Concentrations of 10–60% in oxygen are used, with wide variability in individual response (32). Onset of analgesia is rapid, as is termination of the effect once administration ceases (40). Psychomotor effects have also been studied (61). During the inhalation of 30% end-tidal nitrous oxide, impairment of word recall, the ability to do arithmetic problems, and eye–hand coordination are seen. Impairment is maximal 7 min after beginning inhalation and it remains at that level for the half-hour of gas administration. Subjects report a significant increase in physical and mental sedation and in relief of tension (relaxation). Recovery of normal function is complete 22 min after administration ceases. An appropriate period of postanesthetic supervision is, therefore, necessary for any ambulatory patient after nitrous oxide inhalation.

It should be remembered that analgesia generated with a fixed percentage of nitrous oxide decreases with increasing altitude. This is directly related to the reduced partial pressure of nitrous oxide at a lower total atmospheric pressure. At sea level, inhalation of 50% nitrous oxide generates sufficient analgesia to increase tibial pressure pain threshold 71.5% (52). In the same subjects, 50% nitrous oxide at 1460 m altitude (630 mm Hg in a pressure chamber) produces only a 40% increase, and at 3300 m (518 mm Hg) a 19% increase in tibial pressure pain threshold.

The actual percentage of an inhaled agent reaching the patient, and therefore level of analgesia obtainable, depends on the method of administration. Lichtenthal et al. (71) measured the efficiency of several administration systems by comparing the nitrous oxide concentration delivered to the system to the steady-state end-expiratory concentration in healthy subjects. Fifty percent nitrous oxide in oxygen was delivered to all administration systems. Nasal prongs at 7–8 L/min are only 18% efficient, generating an end-expired concentration of only 9%. A rebreathing mask, such as might be used during regional anesthesia, is 34% efficient, generating an end-expired concentration of 17%. To achieve 95–98% efficiency, a tight-fitting nonrebreathing mask is needed. The effect of an inhaled anesthetic using a dental-type nasal mask also depends on what fraction of inhalation is through the nose and on how much agent is entrained through the nose during oral respiration.

Patient-controlled self-administration of nitrous oxide or methoxyflurane has also been used to provide supplemental analgesia and sedation. Inhalers are available that will deliver 0.3–0.9% methoxyflurane in air (17), or 50% nitrous oxide in oxygen either premixed (105) or from tandem cylinders (39). A potential safety advantage of these devices is the need for patient cooperation in maintaining a tight mouthpiece or mask seal in order to receive anesthetic (17,105,110). This is intended to limit excessive anesthesia with resultant risks of excitement, as well as vomiting and aspiration. Such a potential advantage can, of course, be lost, as by propping the inhaler on a pillow (17). Furthermore, methoxyflurane inhalers are able to deliver concentrations of several times 1 MAC (48), sufficient to produce surgical anesthesia if inspired continuously. Patient-controlled devices are intended to be safe enough to use without an anesthesiologist present. However, the patient receiving self-administered inhalation analgesia still requires a trained individual in constant attendance; this attendant must terminate or decrease the anesthetic if drowsiness, confusion, or excitement develops. Devices for self-administered inhalation analgesia should not be used in "local rooms" of an ambulatory surgery suite without such precautions.

Because the degree of analgesia obtained is strongly influenced by the expectation of pain or its relief, it is not surprising that when patients are given the suggestion that nitrous oxide causes an enhanced sensitivity and awareness of body sensations, pain responses are actually heightened during gas inhalation (31). On the other hand, establishing the expectation that nitrous oxide is an effective analgesic reduces perceived pain. Anxiety and expectation of pain can also be reduced by eliminating stressful environments. More subjective relief and decreased anxiety are obtained using the same 15–45% inhaled nitrous oxide if dental stimulation is performed in a pain-research laboratory rather than in a dental clinic (32).

Side-effects of nitrous oxide inhalation analgesia have been reported. Lichtenthal et al. (71) reported that concentrations of over 30% sometimes cause excitement. Stewart et al. (105), in evaluating 50% nitrous oxide in oxygen, reported a 20.6% incidence of minor side-effects including nausea or vomiting (5.7%), dizziness or lightheadedness (10.3%), excitement (3.7%), and numbness (0.3%). These authors do not include the 7.6% of patients who become drowsy or lightly asleep as complications. Oversedation can, however, eliminate one of the advantages of inhalation analgesia: the preservation of airway reflexes. Twenty percent of patients breathing 50% nitrous oxide in oxygen through a nasal mask aspirated dye placed in the mouth during simulated dental treatment (97).

In summary, inhalation analgesia to supplement ambulatory procedures may be obtained by using approximately 30–50% nitrous oxide or 0.5% enflurane. Undesired side effects, impairment of psychomotor abilities, and sometimes amnesia can occur at these doses. Care must be taken to avoid unintentional general anesthesia and its potential complications.

The author wishes to thank Arlene C. Moldoff for expert secretarial assistance.

## References

1. Abboud TK, Shnider SM, Wright RG, et al. Enflurane analgesia in obstetrics. Anesth Analg 1981;60:133–7.
2. Abramowitz MD, Oh TH, Epstein BS, Ruttimann UE, Friendly DS. The antiemetic effect of droperidol following outpatient strabismus surgery in children. Anesthesiology 1983;59:579–83.
3. Adams AP, Pybus DA. Delayed respiratory depression after use of fentanyl during anaesthesia. Br Med J 1978;1:278–9.
4. Andree RA. Sudden death following naloxone administration. Anesth Analg 1980;59:782–4.
5. Aun C, Flynn PJ, Richards J, Major E. A comparison of midazolam and diazepam for intravenous sedation in dentistry. Anaesthesia 1984;39:589–93.
6. Baird ES, Hailey DM. Delayed recovery from a sedative: correlation of the plasma levels of diazepam with clinical effects after oral and intravenous administration. Br J Anaesth 1972;144:803–8.
7. Becker LD, Paulson BA, Miller RD, Severinghaus JW, Eger EI. Biphasic respiratory depression after fentanyl-droperidol or fentanyl alone used to supplement nitrous oxide anesthesia. Anesthesiology 1976;44:291–6.
8. Bidwai AV, Stanley TH, Rogers C, Riet EK. Reversal of diazepam-induced postanesthetic somnolence with physostigmine. Anesthesiology 1979;51:256–9.
9. Bovill JG, Sebel PS, Blackburn CL, Heykants J. The pharmacokinetics of alfentanil (R39209): a new opioid analgesic. Anesthesiology 1982;57:439–43.
10. Briggs RM, Ogg MJ. Patients' refusal of surgery after Innovar premedication. Plast Reconstr Surg 1973;51:158–61.
11. Brook AH, Major E, Winder M, Berman DS. Inhalation sedation — an adjunct to improved dental care: preliminary communication. J Royal Soc Med 1979;72:756–60.
12. Catchlove RFH, Kafer ER. The effects of diazepam on the ventilatory response to carbon dioxide and on steady-state gas exchange. Anesthesiology 1971;34:9–13.
13. Christensen KN, Huttel M. Naloxone does not antagonize diazepam-induced sedation. Anesthesiology 1979;51:187.
14. Christian CM, Waller JL, Moldenhauer CC. Postoperative rigidity following fentanyl anesthesia. Anesthesiology 1983;58:275–7.
15. Clarke RSJ. New drugs—boon or bane? Premedication and intravenous induction agents. Can Anaesth Soc J 1983;30:166–73.
16. Coe V, Shafer A, White PF. Techniques for administering alfentanil during outpatient anesthesia—a comparison with fentanyl. Anesthesiology 1983;59:A347.
17. Cohen SE. Inhalation analgesia and anesthesia for vaginal delivery. In: Shnider SM, Levinson G, eds. Anesthesia for obstetrics. Baltimore, MD: Williams and Wilkins, 1979:121–38.
18. Cohen SE, Woods WA, Wyner J. Antiemetic efficacy of droperidol and metoclopramide. Anesthesiology 1984;60:67–9.
19. Connor JT, Katz RL, Bellville JW, Graham C, Pagano R, Dorey F. Diazepam and lorazepam for intravenous surgical premedication. J Clin Pharmacol 1978;18:285–92.
20. Connor JT, Katz RL, Pagano RR, Graham GW. RO 21-3981 for intravenous surgical premedication and induction of anesthesia. Anesth Analg 1978;57:1–5.
21. Cook TL, Smith M, Winter PM, Starkweather JA, Eger EI. Effect of subanesthetic concentrations of enflurane and halothane on human behavior. Anesth Analg 1978;57:434–40.
22. Cox HD, Deshon GE, Mittemeyer BT, Condon B, Balance D. Ataralgesia in outpatient urology. Urology 1977;9:164–9.
23. deJong RH, Heavner JE. Diazepam prevents local anesthetic seizures. Anesthesiology 1971;34:523–31.
24. Dixon J, Power SJ, Grundy EM, Lumley J, Morgan M. Sedation for local anaesthesia. Comparison of intravenous midazolam and diazepam. Anaesthesia 1984;39:372–6.
25. Doenicke A, Suttmann H, Kugler J, Kapp W, Wolf R. Pilot study of a benzodiazepine antagonist. Br J Anaesth 1982;54:1131.
26. Dundee JW, McGowan WAW, Lilburn JK, McKay AC, Hegarty JE. Comparison of the actions of diazepam and lorazepam. Br J Anaesth 1979;51:439–46.
27. Dundee JW, Pandit SK. Anterograde amnesic effects of pethidine, hyoscine and diazepam in adults. Br J Pharmacol 1972;44:140–4.
28. Dundee JW, Samuel IO, Toner W, Howard PJ. Midazolam: a water-soluble benzodiazepine. Anaesthesia 1980;35:454–8.
29. Dundee JW, Wilson DB. Amnesic action of midazolam. Anaesthesia 1980;35:459–61.
30. Dupre LJ, Stieglitz P. Extrapyramidal syndromes after pre-

medication with droperidol in children. Br J Anaesth 1980;52:831–3.

31. Dworkin SF, Chen ACN, LeResche L, Clark DW. Cognitive reversal of expected nitrous oxide analgesia for acute pain. Anesth Analg 1983;62:1073–7.

32. Dworkin SF, Schubert MM, Chen ACN, Clark DW. Analgesic effects of nitrous oxide with controlled painful stimuli. JADA 1983;107:581–5.

33. Egbert LD, Battit GE, Welch CE, Bartlett MK. Reduction of postoperative pain by encouragement and instruction of patients. N Engl J Med 1964;270:825–7.

34. Eger EI, Guadagni NP. Halothane uptake in man at constant alveolar concentration. Anesthesiology 1963;24:299–304.

35. Ellis RF, Wilson J. An assessment of droperidol as a premedicant. Br J Anaesth 1972;44:1288–90.

36. Ferrari HA, Stephen CR. Neuroleptanalgesia: pharmacology and clinical experiences with droperidol and fentanyl. South Med J 1966;59:815–20.

37. Fine J, Finestone SC. A comparative study of the side-effects of butorphanol, nalbuphine and fentanyl. Anesthesiol Rev 1981;8:13–7.

38. Fitzal S, Knapp-Groll E, Ilias W, Scherzer W, Tonczar L. Vergleich zweier Pramedikations methoden: psychische, sedative und somatische Reaktionen. Anaesthesist 1979;28:572–7.

39. Flomenbaum N, Gallagher EJ, Eagen K, Jacobsen S. Self-administered nitrous oxide: an adjunct analgesic. JACEP 1979;8:95–7.

40. Forster A, Gardaz JP, Suter PM, Gemperle M. I.V. midazolam as an induction agent for anaesthesia: a study in volunteers. Br J Anaesth 1980;52:907–11.

41. Gale GD. Recovery from methohexitone, halothane and diazepam. Br J Anaesth 1976; 48:691–8.

42. Gamble JAS, Kawar P, Dundee JW, Moore J, Briggs LP. Evaluation of midazolam as an intravenous induction agent. Anaesthesia 1981;36:868–73.

43. Garber JG, Ominsky AJ, Orkin FK, Quinn P. Physostigmine-atropine solution fails to reverse diazepam sedation. Anesth Analg 1980;59:58–60.

44. Griffin CG, Campbell VD, Jones R. Nitrous-oxygen sedation for minor surgery. JAMA 1981;245:2411–3.

45. Gross JB, Smith L, Smith TC. Time course of ventilatory response to carbon dioxide after intravenous diazepam. Anesthesiology 1982;57:18–21.

46. Hegarty JE, Dundee JW. Sequelae after the intravenous injection of three benzodiazepines—diazepam, lorazepam, and flunitrazepam. Br Med J 1977;2:1384–5.

47. Herr GP, Conner JT, Katz RL, Dorey F, L'Armand J, Schehl D. Diazepam and droperidol as i.v. premedicants. Br J Anaesth 1979;51:537–42.

48. Holl JW, Shnider SM. Methoxyflurane concentrations from the Cyprane inhaler. Anesthesiology 1967;28:770–1.

49. Hudson RJ, Stanski DR. Metabolism vs. redistribution of fentanyl and alfentanil. Anesthesiology 1983;59:A243.

50. Indresano AT, Rooney TP. Outpatient management of mentally handicapped patients undergoing dental procedures. JADA 1981;102:328–30.

51. Iwamoto K, Schwartz H. Antiemetic effect of droperidol after ophthalmic surgery. Arch Ophthalmol 1978;96:1378–9.

52. James MFM, Manson EDM, Dennett JE. Nitrous oxide analgesia and altitude. Anaesthesia 1982;37:285–8.

53. Janssen PAJ, Niemegeers CJE, Schellekens KHL, Verbruggen FJ, Van Nueten JM. The pharmacology of dehydrobenzperidol, a new potent and short acting neurolept agent chemically related to haloperidol. Arzneim Forsch 1963;13:205–11.

54. Jensen S, Huttel MS, Schou Olesen A. Venous complications after i.v. administration of diazemuls (diazepam) and dormicum (midazolam). Br J Anaesth 1981;53:1083–5.

55. Job CA, Fernandez MA, Dorph DJ, Betcher AM. Inguinal hernia repair. Comparison of local, epidural, and general anesthesia. NY State J Med 1979;79:1730–3.

56. Karhunen U, Orko R. Nausea and vomiting after local anesthesia for cataract extraction in elderly female patients — effect of droperidol premedication. Ophthal Surg 1981;12:810–2.

57. Kay B. Alfentanil. Br J Anaesth 1982;54:1011–3.

58. Kay B. Postoperative pain relief. Use of an on-demand analgesia computer (ODAC) and a comparison of the rate of use of fentanyl and alfentanyl. Anaesthesia 1981;36:949–51.

59. Klotz U, Antonin KH, Bieck PR. Pharmacokinetics and plasma binding of diazepam in man, dog, rabbit, guinea pig, and rat. J Pharmacol Exp Ther 1976;199:67–73.

60. Klotz U, Avant GR, Hoyumpa A, Schenker S, Wilkinson GR. The effects of age and liver disease on the disposition and elimination of diazepam in adult man. J Clin Invest 1975;55:347–59.

61. Korttila K, Ghoneim MM, Jacobs L, Mewaldt SP, Petersen RC. Time course of mental and psychomotor effects of 30 per cent nitrous oxide during inhalation and recovery. Anesthesiology 1981;54:220–6.

62. Korttila K, Kauste A, Auvinen J. Comparison of domperidone, droperidol, and metoclopramide in the prevention and treatment of nausea and vomiting after balanced general anesthesia. Anesth Analg 1979;58:396–400.

63. Korttila K, Linnoila M. Psychomotor skills related to driving after intramuscular administration of diazepam and meperidine. Anesthesiology 1975;42:685–91.

64. Korttila K, Linnoila M. Recovery and skills related to driving after intravenous sedation: dose–response relationship with diazepam. Br J Anaesth 1975;47:457–63.

65. Korttila K, Linnoila M. Skills related to driving after intravenous diazepam, flunitrazepam or droperidol. Br J Anaesth 1974;46:961–9.

66. Korttila K, Mattila MJ, Linnoila M. Prolonged recovery after diazepam sedation: the influence of food, charcoal ingestion and injection rate on the effects of intravenous diazepam. Br J Anaesth 1976;48:333–40.

67. Kreienbuhl G. Der Einfluss der Pramedikation auf die subjektiven post-anaesthetischen Beschwerden bei ambulanten (Tagesklinik-) Patienten. Anaesthesist 1980;29:421–4.

68. Kromann B, Jorgensen J, Larsen S. Diazepam in an oil emulsion. Anesth Analg 1982;61:544.

69. Lee CM, Yeakel AE. Patient refusal of surgery following Innovar$^{(R)}$ premedication. Anesth Analg 1975;54:224–6.

70. Lewis M, Forster A, Suter PM, Gemperle M. Clinical and hemodynamic effects of a specific benzodiazepine antagonist (RO 15-1788) after open heart surgery. Anesthesiology 1984;61:A61.

71. Lichtenthal P, Philip J, Sloss LJ, Gabel R, Lesch M. Administration of nitrous oxide in normal subjects. Chest 1977;72:316–22.

72. Loeser EA, Bennett G, Stanley TH, Machin R. Comparison of droperidol, haloperidol and prochlorperazine as postoperative antiemetics. Can Anaesth Soc J 1979;26:125–7.

73. Maduska LA, Tielens DR. Plasma and cerebrospinal fluid fluoride levels following the obstetrical use of methoxyflurane analgesia. Anesthesiol Rev 1976;3:40–1.

74. Mandelli M, Tognoni G, Garattini S. Clinical pharmacokinetics of diazepam. Clin Pharmacokinet 1978;3:72–91.

75. McClain DA, Hug CC. Intravenous fentanyl kinetics. Clin Pharmacol Ther 1980;28:106–14.

76. McClure JH, Brown DT, Wildsmith JAW. Comparison of the i.v. administration of midazolam and diazepam as sedation during spinal anaesthesia. Br J Anaesth 1983;55:1089–93.

77. McDonnell TE, Bartkowski RR, Williams JL. $ED_{50}$ of alfentanil for induction of anesthesia of unpremedicated young adults. Anesthesiology 1984;60:136–40.

78. McKenzie R, Wadhwa RK, Lim Uy NT, et al. Antiemetic effectiveness of intramuscular hydroxyzine compared with intramuscular droperidol. Anesth Analg 1981;60:783–8.

79. Meridy HW. Criteria for selection of ambulatory surgical patients and guidelines for anesthetic management: a retrospective study of 1553 cases. Anesth Analg 1982;61:921–6.

80. Mikkelsen H, Hoel TM, Bryne H, Krohn DC. Local reactions after i.v. injections of diazepam, flunitrazepam, and isotonic saline. Br J Anaesth 1980;52:817–9.

81. Morrison JD, Clarke RSJ, Dundee JW. Studies of drugs given before anesthesia. XXI: Droperidol. Br J Anaesth 1970;42:730–5.

82. Mortensen PT. Droperidol (Dehydrobenzperidol)(R): postoperative anti-emetic effect when given intravenously to gynaecological patients. Acta Anaesth Scand 1982;26:48–52.

83. Niemegeers CJE, Janssen PAJ. Alfentanil (R 39209), a particularly short-acting morphine-like narcotic for intravenous use in anaesthesia. Drug Devel Res 1981;1:83–8.

84. Nikki P, Pohjola S. Nausea and vomiting after ocular surgery. Acta Ophthal 1972;50:525–31.

85. Pagano RR, Graham CW, Galligan M, Conner JT, Katz RL. Histopathology of veins after intravenous lorazepam and RO 21-3981. Can Anaesth Soc J 1978;25:50–2.

86. Pandit SK, Heisterkamp DV, Cohen PJ. Further studies of the anti-recall effect of lorazepam: a dose–time–effect relationship. Anesthesiology 1976;45:495–500.

87. Patrick M, Eager B, Toft DF, Sebel PS. Alfentanil supplemented anesthesia for short procedures: a double blind comparison with fentanyl. Anesthesiology 1983;59:A346.

88. Patton CM, Moon MR, Dannemiller FJ. The prophylactic antiemetic effect of droperidol. Anesth Analg 1974;53:361–4.

89. Philip JH. GAS MAN — Understanding anesthesia uptake and distribution. Menlo Park, CA: Addison-Wesley, 1984.

90. Plowman PE, Thomas WJW, Thurlow AC. Cardiac dysrhythmias during anaesthesia for oral surgery. Anaesthesia 1974;29:571–5.

91. Prokocimer P, Delavault E, Rey F, Lefevre P, Mazze RI, Desmonts JM. Effects of droperidol on respiratory drive in humans. Anesthesiology 1983;59:113–6.

92. Prough DS, Roy R, Bumgarner J, Shannon G. Acute pulmonary edema in healthy teenagers following conservative doses of intravenous naloxone. Anesthesiology 1984;60:485–6.

93. Purkis IE. Factors that influence postoperative vomiting. Can Anaesth Soc J 1964;11:335–53.

94. Rigg JRA, Goldsmith CH. Recovery of ventilatory response to carbon dioxide after thiopentone, morphine and fentanyl in man. Can Anaesth Soc J 1976;23:370–82.

95. Rita L, Goodarzi M, Seleny F. Effect of low dose droperidol on postoperative vomiting in children. Can Anaesth Soc J 1981;28:259–62.

96. Rosow CE, Latta WB, Keegan CR, et al. Alfentanil and fentanyl in short surgical procedures. Anesthesiology 1983;59:A345.

97. Rubin J, Brock-Utne JG, Greenberg M, Bortz J, Downing JW. Laryngeal incompetence during experimental "relative analgesia" using 50% nitrous oxide in oxygen. Br J Anaesth 1977;49:1005–7.

98. Ryder W, Wright PA. Halothane and enflurane in dental anaesthesia. Anaesthesia 1981;36:492–7.

99. Sainpy D, Boileau S, Vicari F. Etude comparative du midazolam et du diazepam intraveineux comme agents de sedation en endoscopie digestive. Ann Fr Anesth Reanim 1984;3:177–80.

100. Scamman FL. Fentanyl–$O_2$–$N_2O$ rigidity and pulmonary compliance. Anesth Analg 1983;62:332–4.

101. Schou Oleson A, Huttel MS. Local reactions to i.v. diazepam in three different formulations. Br J Anaesth 1980;52:609–11.

102. Sinclair ME, Cooper GM. Alfentanil and recovery. Anaesthesia 1983;38:435–7.

103. Sokoll MD, Hoyt JL, Gergis SD. Studies in muscle rigidity, nitrous oxide, and narcotic analgesic agents. Anesth Analg 1972;51:16–20.

104. Stanski DR, Hug CC. Alfentanil—a kinetically predictable narcotic analgesic. Anesthesiology 1982;57:435–8.

105. Stewart RD, Paris PM, Stoy WA, Cannon G. Patient-controlled inhalational analgesia in prehospital care: a study of side-effects and feasibility. Crit Care Med 1983;11:851–5.

106. Stirt JA. Aminophylline is a diazepam antagonist. Anesth Analg 1981;60:767–8.

107. Stoeckel H, Hengstmann JH, Schuttler J. Pharmacokinetics of fentanyl as a possible explanation for recurrence of respiratory depression. Br J Anaesth 1979;51:741–5.

108. Stoeckel H, Schuttler J, Magnussen H, Hengstmann JH. Plasma fentanyl concentrations and the occurrence of respiratory depression in volunteers. Br J Anaesth 1982;54:1087–95.

109. Taff RH. Pulmonary edema following naloxone administration in a patient without heart disease. Anesthesiology 1983;59:576–7.

110. Thal ER, Montgomery SJ, Atkins JM, Roberts BG. Self-administered analgesia with nitrous oxide. JAMA 1979;242:2418–9.

111. Thompson DG, Evans SJ, Murray RS, Lennard-Jones JE, Cowan RE, Wright JT. Patients appreciate premedication for endoscopy. Lancet 1980;2:469–70.

112. Tracey JA, Holland AJC, Unger L. Morbidity in minor gynaecological surgery: a comparison of halothane, enflurane, and isoflurane. Br J Anaesth 1982;54:1213–5.

113. Wetchler BV, Collins IS, Jacob L. Antiemetic effects of droperidol on the ambulatory surgery patient. Anesthesiol Rev 1982;9:23–6.

114. White PF. Use of continuous infusion versus intermittent bolus administration of fentanyl or ketamine during outpatient anesthesia. Anesthesiology 1983;59:294–300.

115. Willatts DG, Harrison AR, Groom JF, Crowther A. Cardiac arrhythmias during outpatient dental anaesthesia: comparison of halothane with enflurane. Br J Anaesth 1983;55:399–403.

116. Winning TJ, Brock-Utne JG, Downing JW. Nausea and vomiting after anesthesia and minor surgery. Anesth Analg 1977;56:674–7.

## Clinical Reports

# Development of Resistance to Pancuronium in Adult Respiratory Distress Syndrome

Deborah L. Callanan, MD

Muscle relaxants are being used not only more frequently but also for longer periods as improved techniques in mechanical ventilation produce longer survival of patients with severe respiratory disease. It is often helpful to these patients both to minimize their work of breathing in order to decrease oxygen consumption and to decrease the inflating pressures generated in order to possibly lower the risk of barotrauma (1). Typically, repeated doses or continuous infusions of a nondepolarizing muscle relaxant such as pancuronium have been effective in providing paralysis of the respiratory muscles (2). In this report, I present the case of a patient who became unresponsive to the muscle relaxant effects of pancuronium on the sixth day it was used.

## Case Report

A 15-yr-old, 50 kg girl was admitted to the Hospital of the Medical College of Pennsylvania on August 8, 1984 after ingesting approximately 3 g of doxepin. She was reponsive only to deep pain on arrival in the emergency room. A tracheal tube was inserted shortly thereafter for management of ventilation and for airway protection. She was treated with repeated gastric lavages and charcoal administration for the next 24 hours. Initial arterial blood–gas analysis taken while the patient was breathing 100% $O_2$ on a Bear ventilator with a tidal volume of 650 ml at a rate of 15 breaths/min showed a $P_{O_2}$ of 387 mm Hg, $P_{CO_2}$ of 30 mm Hg, and pH 7.45. The initial chest x-ray was normal, although the tip of the endotracheal tube was at the carina. On admission to the pediatric intensive care unit, the endotracheal tube was suctioned with return of thick brown secretions. A repeat chest x-ray showed a dense right upper lobe, a suggestion of increased interstitial markings in the remainder of the right lung, and good position of the endotracheal tube. Arterial blood–gas analysis showed a $P_{O_2}$ of 99 mm Hg with an $F_{I_{O_2}}$ of 0.6. Therapy with PEEP was begun at 5 cm $H_2O$

Thirty-six hours after admission, the patient was intermittently alert and able to answer questions by moving her head. Her chest x-ray, however, showed a bilateral glassy appearance compatible with adult respiratory distress syndrome, and her ventilatory requirements included a PEEP of 10 cm $H_2O$ and an $F_{I_{O_2}}$ of 0.6 to maintain a $P_{O_2}$ of 97 mm Hg. On the third hospital day, a catheter was inserted into the left subclavian vein. This was complicated by development of a left tension pneumothorax and cyanosis of the left hand. The pneumothorax was treated with a thoracostomy tube, but a continuous air leak remained with development of a pneumomediastinum and subcutaneous emphysema. On August 11, 1984, the patient underwent arteriography, and subsequently thrombectomy and embolectomy were performed to remove clots from the left subclavian artery and vein and the left brachial artery. During the course of that day, she became progressively more difficult to ventilate because of motor activity, so she was sedated with a total of 35 mg diazepam and given pancuronium bromide. Because the severity of her lung disease made it desirable to minimize her $O_2$ consumption, it was elected to continue muscle paralysis postoperatively. Between August 11 and 17, she received 310 mg intravenous pancuronium with individual doses ranging from 4 to 8 mg. The apnea produced lasted 75–120 min after these doses of pancuronium. She was also given diazepam and morphine for sedation.

---

Received from the Department of Pediatrics, Medical College of Pennsylvania, Philadelphia, Pennsylvania. Accepted for publication June 3, 1985.

Address correspondence to Dr. Callanan, Department of Pediatrics, Medical College of Pennsylvania, 3300 Henry Avenue, Philadelphia, PA 19129.

© 1985 by The International Anesthesia Research Society

On August 17, she received 8 mg of pancuronium at 10 AM. She also received her usual sedation of 2.5 mg of diazepam at 7 and 11 AM and 2 mg of morphine at 8 and 10 AM. Because of spontaneous ventilatory efforts, another dose of 8 mg of pancuronium was given at 11:30 AM. The drug was given through the proximal port of a Swan–Ganz catheter from which blood could be aspirated freely. There was no apparent effect on her respiratory effort. A supplemental dose of 4 mg pancuronium was given without effect. At 12 noon she had onset of tachycardia (150 beats/min) and hypertension (170–200/90 mm Hg). Sedation with 4 mg morphine produced better synchronization of lung inflation with the ventilator, but respiratory effort was still present. The pancuronium was obtained from two different vials, and neither expiration date had been reached. The mode of ventilation was changed to synchronized intermittent mandatory ventilation in an attempt to deliver adequate tidal volumes, but the respiratory rate had to be increased from 24 to 45 breaths/min to coordinate with her respiratory drive. The hypertension and tachycardia resolved. Subsequent use of pancuronium and sedation failed to produce apnea. The patient expired from respiratory failure on August 19, 1984.

Other medications used in this patient included, in addition to a parenteral nutrition solution containing 35% glucose and 5% amino acids, Intralipid, diphenylhydantoin, cefotaxime, clindamycin, morphine sulfate, diazepam, heparin, cimetidine, and aspirin. Her doxepin level was 1090 ng/ml on August 8, 520 ng/ml on August 9, and only 30 ng/ml on August 15 (therapeutic range is 110–240 ng/ml), so doxepin should not have had any interaction with the pancuronium effect by August 17. Two 10-mg doses of furosemide had been given at 3 AM and 8 AM on August 17. Urine output was 1762 cc/24 hr in this 50-kg girl.

Laboratory studies on August 16 showed a total protein, 5.6 g/dl; albumin, 2.8 g/dl; calcium, 7.5 mg/dl; phosphorus, 4.2 mg/dl; alkaline phosphatase, 116 U/L; and total bilirubin, 2.3 mg/dl. Hemoglobin was 11.4 g/dl, white blood cells (WBC) 27,600/mm$^3$, and platelets were 210,000. Prothrombin time was 23 sec (control 12), and partial thromboplastin time was 72 sec with a control of 34.

## Discussion

Correspondence with Organon, the manufacturer of pancuronium, revealed no previous reports of this phenomenon. Possible mechanisms proposed for this patient's unresponsiveness to the neuromuscular blockade include the following.

The affinity of the neuromuscular cholinergic receptors for pancuronium decreased dramatically.

Pancuronium became bound to an antibody or some other substance that was not present in the plasma at the start of treatment.

An enzyme capable of rapidly metabolizing pancuronium developed in the course of treatment, or the pancuronium was precipitated by some exogenous material administered to this patient.

Increased liver metabolism or urinary excretion of pancuronium occurred.

The number of acetylcholine receptors increased.

Decreased receptor affinity may have occurred. Although the patient became tachycardic and hypertensive after the ineffective dose of pancuronium, it seems likely that this was not due to the cardiovascular effects of the drug but rather to the anxiety and stress associated with her marked incoordination with the ventilator. The hypertension and tachycardia did resolve with the change to synchronized intermittent mandatory ventilation (IMV) and increased doses of sedatives.

Binding to some material in the plasma may have occurred. Usually the percentage of pancuronium bound to protein is clinically insignificant (3, p 205). However, this patient was receiving an intravenous amino acid solution. Perhaps this might react with pancuronium differently than do the usual plasma proteins.

Increased urinary excretion seems unlikely because even with furosemide, the patients' urine output was normal. There was mild evidence of liver dysfunction with an increase in the direct bilirubin. The autopsy showed passive congestion of the liver. Increased liver uptake thus seems unlikely.

This patient received multiple drugs. Although clindamycin is reported to prolong the neuromuscular blockade, none of these drugs is reported to antagonize the block (3, p 208).

A marked change in ventilatory status could have altered the respiratory drive and thus the response of respiratory muscles to pancuronium. However, the blood–gas analyses before the effective and ineffective doses of pancuronium were remarkably similar. At 10 AM, $P_{O_2}$ was 74 mm Hg, $P_{CO_2}$ was 46 mm Hg, and pH 7.46. At 11 AM, $P_{O_2}$ was 64 mm Hg, $P_{CO_2}$ 45 mm Hg, and pH 7.46. Thus it seems highly unlikely that a chemical stimulus to ventilation played a role in the changed response to pancuronium.

Burn patients have been reported to need larger than usual doses of pancuronium and other muscle relaxants. The mechanism for this is thought to be an increase in the number of acetylcholine receptors or altered affinity of the relaxants for these receptors (4). The presence of large quantities of fluid in the physiologic third space is a factor common to burn patients and those with adult respiratory distress syndrome who have altered cardiac return due to high levels of positive and expiratory pressure. It is possible that pancuronium may be trapped in this space and be unavailable for physiologic activity. Resistance to pancuronium has also been reported in an asthmatic patient, but he was receiving aminophylline and hydrocortisone, both of which can reverse the neuromuscular blockade (5).

Because of the complex nature of this patient's illness, she received a large number of medications that may singly or in combination have altered her response to pancuronium. She had multisystem dysfunction that also may have affected her response. The failure of pancuronium to produce respiratory paralysis made her ventilatory status far more difficult to manage. Curare was not used in this patient because it was feared that any hypotension produced might upset the precarious balance between cardiac output and the impaired venous return which resulted from 20 cm $H_2O$ of PEEP. No other muscle relaxants were tried because synchronized IMV and increased sedation were adequate alternatives to paralysis in the terminal phase of her disease. Clinicians should be aware of the potential for muscle relaxant failure so that alternate strategies in respiratory management can be planned.

In summary, a 15-yr-old with adult respiratory distress syndrome became resistant to the effects of pancuronium on the sixth day of its use. This made control of her ventilation much more difficult. Possible mechanisms for the failure of pancuronium to produce muscle paralysis are proposed. Clinicians should consider the possibility of resistance developing to muscle relaxants so that other modes of managing ventilation can be planned.

Francis F. Foldes, MD., provided helpful suggestions and reviewed the manuscript.

## References

1. Bishop MJ. Hemodynamic and gas exchange effects of pancuronium bromide in sedated patients with respiratory failure. Anesthesiology 1984;60:369–71.
2. Clyburn PA, Marshall RD. Control of ventilation by continuous infusion of pancuronium bromide. Anaesthesia 1981;36:860–2.
3. Dripps RD, Eckenhoff JE, Vandam LD. Introduction to anesthesia: the principles of safe practice, 5th ed. Philadelphia:W.B. Saunders Co., 1977.
4. Yamashita M, Shiga T, Matsuki A, Oyama T. Unusual resistance to pancuronium in severely burned patients. Can Anaesth Soc J 1982;29:630–1.
5. Azar I, Kumar D, Betcher AM. Resistance to pancuronium in an asthmatic patient treated with aminophylline and steroids. Can Anaesth Soc J 1982;29:280–2.

# Cardiac Arrest in a Child with an Anterior Mediastinal Mass

H. Levin, MB, BCh, S. Bursztein, MD, and M. Heifetz, MD

Mediastinal masses can occasionally cause compression and obstruction of the trachea and main bronchi (1–4). They may cause superior vena cava obstruction (5,6), cardiac compression, and, rarely, mechanical compression on the pulmonary artery (7).

## Case Report

A six-yr-old boy was admitted complaining of general malaise, loss of weight, and shortness of breath. His mother said that when he was in the supine position, the child became blue. The child had had no prior hospital admissions and apparently had been well previously.

On examination in the supine position, he was dyspneic and mildly cyanotic. His neck veins were moderately distended. His face was not swollen, and his eyes did not bulge. A few immobile cervical lymph nodes were palpable in his neck. Examination of the upper airway and chest were essentially normal, with no signs of obstruction, and both lung fields were clear. When he sat up, the child improved markedly. Chest x-ray showed a large anterior mediastinal mass. Tomography was not performed. Blood count was normal. Hodgkin's type lymphoma was the presumptive diagnosis, and the child was scheduled for a cervical lymph node biopsy to make a definitive diagnosis. He was premedicated with 40 mg of meperidine and 0.2 mg of scopolamine 45 min before arriving in the operating room. When examined in the operating room, the child was sedated, supine, mildly cyanotic, and obviously hyperpneic. The lungs appeared normal.

He was preoxygenated for 5 min before being administered 100 mg of thiopental and 20 mg of succinyldicholine. Tracheal intubation was performed without difficulty. In spite of the administration of 100% $O_2$, the child remained cyanotic. The position of the tracheal tube and lung fields were reexamined. There were good breath sounds in both lungs. After approximately 5 min he started breathing spontaneously, and his color improved. Halothane, 0.5%, was added to the oxygen. His respiration was assisted (not controlled) throughout the procedure. The lymph node was removed without difficulty. The child was now breathing spontaneously. The tracheal tube was removed, but within a very short period he became deeply cyanotic and hyperpneic. Bradycardia developed. He was immediately reintubated and ventilated with 100% $O_2$. Atropine was given but had no affect. Blood pressure was unrecordable. Again breath sounds in both lungs were good. In spite of further atropine and isoproterenol, cardiac arrest occurred. All resuscitory measures, including external cardiac massage, intracardiac epinephrine, bicarbonate, calcium gluconate, and isoproterenol, proved ineffective. We decided to open the chest and to perform open massage. Immediately upon opening of the chest and upon further injection of epinephrine, the heart restarted. His color became pink, and his blood pressure quickly rose to 80 torr. His pupils, however, remained widely dilated and nonreactive. The chest was closed in the usual manner and a left underwater drain was inserted into the pleural cavity. He had a $Pa_{O_2}$ of 99.5 mm Hg ($F_{I_{O_2}}$, 1.0). He showed signs of spontaneous respirations but remained unconscious. He was transferred to the intensive care unit where he was ventilated using a volume cycled MA.1. ventilator. For 2 hr there was no change in his condition: blood pressure, 80 torr; pulse, 130 beats/min; $Pa_{O_2}$ 96 mm Hg; $Pa_{CO_2}$, 37 mm Hg; pH, 7.37. He passed no urine. Cardiac arrest suddenly occurred again and, in spite of all resuscitory measures, he died 3 hr after the initial arrest.

On postmortem examination, a large anterior mediastinal mass was found. This proved to be a Hodgkin's lymphoma. The mass impinged upon but did not compress the trachea. It also compressed the main pulmonary artery. On dissection of the trachea, it was found to be patent with no signs of compression from the external mass.

---

Received from the Department of Anesthesia and Intensive Care, Lady Davis Carmel Hospital, Haifa, Israel. Accepted for publication June 4, 1985.

Address correspondence to Dr. Levin, Department of Anesthesia, Lady Davis Hospital, 7 Michael Street, Haifa, Israel, 34 362.

© 1985 by the International Anesthesia Research Society

## Discussion

In reviewing this case, we had great difficulty in understanding why, in spite of a well-controlled airway and good ventilation we were unable to oxygenate the child. Clinically, the child did not have a full-blown superior vena cava syndrome, although the pulmonary artery was compressed by tumor mass. Dyspnea and intolerance of the supine position (1,5–8) may result from compression of the airway by mediastinal masses. However, we were able to ventilate the lungs of this patient easily.

Postmortem examination showed that there was no pressure on the trachea but some compression on the pulmonary artery. We therefore suggest that, when the child was in the supine position, the tumor mass increased compression on the pulmonary artery and perhaps the heart, causing an effective and massive decrease in the right ventricular output. When the child was in the sitting position, compression was decreased and the effective pulmonary flow increased. We treated the child in the supine position with positive pressure ventilation, which possibly further aggravated his condition. This may be explained by the fact that the pressure not only was on the pulmonary arteries but also was compressing the heart. One would expect an acute dilatation of the right side of the heart if the obstruction was affecting the pulmonary arteries. This can be partially relieved by positive pressure ventilation, decreasing the venous return; nevertheless pulmonary flow oxygenation will not improve.

Several authors (1,2,4,5,9) have described the problems that occur secondary to compression of the trachea or bronchi. They emphasize the importance of spontaneous ventilation, the sitting position (8,9), and preoperative irradiation, massive steroid therapy, or both to prevent life-threatening airway complications. The anesthetist has, of course, to be aware of the serious danger of air embolism when a patient is in the sitting position and about to undergo surgical procedures on the neck.

Unlike the superior vena cava syndrome, the pulmonary trunk and main bronchi are more or less encircled by the aortic arch, rendering them less vulnerable to external compression. Therefore, the complication encountered in the present case, although described, is rare.

In 1975, Hall and Friedman described a child with a large anterior mediastinal mass in whom induction of anesthesia was impossible on two occasions because of the development of deep cyanosis. Subsequently they utilized an extracorporeal membrane oxygenator to maintain oxygenation during induction and anesthesia, and immediately upon removal of the tumor, the child was able to oxygenate himself without assistance from the pump. In their article, Hall and Friedman postulate that the tumor mass compressed the pulmonary artery. They suggested that spontaneous ventilation maintained the patency of the pulmonary arteries, perhaps because negative pressure was maintained during inhalation.

The present case demonstrates that not all cases of cyanosis in the presence of anterior mediastinal masses are due to compression of the airway, but may well be due to cardiovascular compression with a decrease in right ventricular output, thus preventing adequate oxygenation. Suggested management includes a thorough preoperative cardiovascular evaluation. If there are cardiovascular problems, local anesthesia should be tried if at all possible (4,8). Alternatively, preoperative irradiation, massive steroid therapy, and anesthesia in the sitting or even face-down position is advised. Spontaneous and noncontrolled ventilation (5,8) should be instituted if at all possible. Should these not be sufficient, then utilization of extracorporeal oxygenation may be warranted.

The patient with an anterior mediastinal mass presents specific problems that should be thoroughly evaluated before submitting the patient to a general anesthetic.

## References

1. Todres IP, Reppelt SM, Walker PF, Griero AC. Management of critical airway obstruction in a child with mediastinal tumor. Anesthesiology 1976;45:100–2.
2. Amaha K, Okutsu Y, Nakamura Y. Major airway obstruction by mediastinal tumor. Br J Anaesth 1973;45:1082–4.
3. Lokich JJ, Goodman R. Superior vena cava syndrome. Clinical management. JAMA 1978;231:58–61.
4. Stanley TH, Weidauer HE. Anesthesia for the patient with cardiac tamponade. Anesth Analg 1973;52:110–4.
5. Neuman GG, Weingarten AE, Abramowitz RM, Kushing LG, Abramson AL, Ladner W. The anesthetic management of the patient with an anterior mediastinal mass. Anesthesiology 1984;60:144–7.
6. Bray RJ, Fernandes FJ. Mediastinal tumor causing airway obstruction in anaesthetized children. Anaesthesia 1982;37:571–5.
7. Hall KD, Friedman M. Extracorporeal oxygenation for induction of anesthesia in a patient with an intrathoracic tumor. Anesthesiology 1975;42:493–5.
8. Mackie AM, Watson CB. Anaesthesia and mediastinal masses. Anaesthesia 1984;39:899–903.
9. Keon TP. Death on induction of anesthesia for cervical node biopsy. Anesthesiology 1981;55:471–2.

ANESTH ANALG
1985;64:1131-3

# Hepatic Necrosis Associated with Herpes Virus after Isoflurane Anesthesia

Nancy A. Fisher, MD, Robert T. Iwata, MD, Edmond I. Eger II, MD, and Edward A. Smuckler, MD

Severe injury of the liver after anesthesia may be attributed to anesthesia, especially in the absence of other documented causes of hepatic damage. Attribution of the injury to the anesthetic is more likely after anesthesia with a halogenated agent because of the known hepatotoxicity of some halogenated anesthetics such as chloroform. However, another cause of injury is viral infection, a cause that often is difficult to document (e.g., non-A, non-B hepatitis). We present a case of severe hepatic injury in which isoflurane was considered a possible cause. This diagnosis was later discarded because of the discovery of invasion of the liver by herpes virus.

## Case Report

On May 13, 1984, a 62-yr-old (weight 46 kg, height 184 cm), quadriplegic man presented with acute pain of the right upper quadrant and flank. Quadriplegia had resulted from poliomyelitis at age 28. Despite this condition, the patient had been in good health and, with assistance, had been able to care for himself. He had no allergies. He had undergone several operations, all before 1950. There was no history of jaundice or liver disease. On admittance to the hospital, the patient was nauseated, diaphoretic, and mildly febrile (37.6°C). Physical examination was unremarkable except for a pectus excavatum and muscle wasting secondary to poliomyelitis.

Right ureteral obstruction and cholelithiasis were demonstrated by x-ray. Chest x-ray was normal, and ECG revealed only a right bundle branch block. Except for a leftward shift of the white cells, other laboratory data were normal (Table 1). The patient was considered to be ASA physical status II.

On May 15, after the patient was premedicated with 0.4 mg of atropine, anesthesia was induced with 250 mg of thiopental. Atracurium (30 mg) was given to facilitate tracheal intubation, and ventilation was controlled. Anesthesia was maintained with nitrous oxide (2 L/min), and oxygen (1 L/min), to which 2% and then 1–1.25% isoflurane was added. Atracurium (10 mg) was given to facilitate closure of the abdomen, and reversal of neuromuscular blockade was accomplished with 30 mg of edrophonium and 0.8 mg of atropine.

A right transperitoneal ureterolithotomy plus cholecystectomy with cholangiograms were accomplished in about 2 hr (duration of anesthesia, 150 min). Blood loss was estimated at 100–300 ml, and no blood was given in the perioperative period before development of hepatic injury. Intraoperative blood pressures were 90–105/65–75 mm Hg. There were no difficulties with surgery except for dilation of the colon that hindered closure of the abdomen. Cultures of the gallbladder and bile did not reveal growth of bacteria.

Recovery initially was uneventful except for ileus and abdominal distension managed with enemas and drainage through a rectal tube, and transient hyponatremia (118 mEq/L) thought to be due to the enemas, nasogastric suction, and hyperalimentation. Peak daily temperatures for the first three postoperative days were 38.4°C, 37.8°C, and 38.0°C. On day 4, temperature increased to a peak of 38.8°C and for the next several days exceeded 39.0°C despite therapy with cefoperazone and amikacin. A chest x-ray and $PaO_2$ value of 58 mm Hg suggested the presence of atelectasis or pneumonia. No growth was obtained from several cultures of blood. Ultrasound examination of the abdomen gave equivocal evidence of abscess formation.

The patient vomited on day 6. On day 9 (May 24) the ileus present initially gave way to diarrhea, which persisted to the day of the patient's death. Blood drawn on day 9 demonstrated hepatic injury (Table 1). Hypotension and diaphoresis occurred on day 10. On day 11, the patient became lethargic and subsequently

---

Received from the Departments of Anesthesia and Pathology, Mercy Medical Center, Roseburg, Oregon, and the Departments of Anesthesia and Pathology, University of California at San Francisco, San Francisco, California. Accepted for publication June 3, 1985.

Address correspondence to Dr. Eger, Department of Anesthesia, University of California, San Francisco, Room 1386 HSE, Third and Parnassus Avenues, San Francisco, CA 94143.

© 1985 by the International Anesthesia Research Society

Table 1. Blood Variables and Temperature Changes

| Postoperative day | WBC (per $\text{mm}^{-3}$) | Segs (%) | Eos (%) | Total bilirubin (mg%) | GGT (IU) | LDH (IU) | SGOT (IU) | Peak temp (°C) |
|---|---|---|---|---|---|---|---|---|
| −2 | 9900 | 83 | 2 | 0.8 | 21 | 150 | 26 | 37.6 |
| 6 | 9300 | 83 | 0 | — | — | — | — | 39.5 |
| 9 | 8200 | 84 | 0 | 0.5 | 102 | > 600 | > 500 | 39.2 |
| 11 | 6500 | 85 | 0 | — | — | — | — | 39.3 |
| 13 | 5600 | 65 | 0 | 1.2 | 207 | > 600 | > 500 | 39.4 |

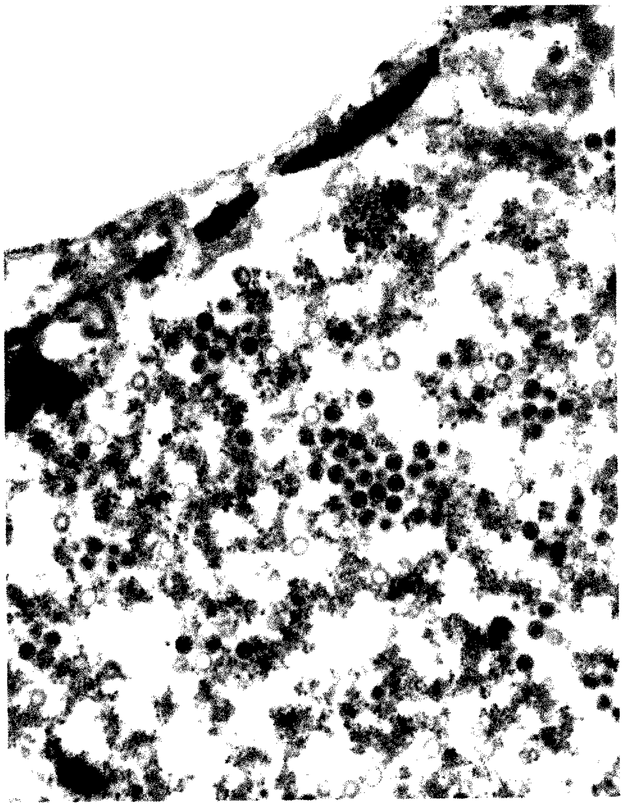


Figure 1. Electron micrograph of postmortem specimen at a magnification of 50,000 showing viral particles in various stages of development within the nucleus of a degenerative liver cell. The unfilled circles are immature or incomplete viral particles; filled black circles with a halo are mature viral particles. The particles are morphologically consistent with a herpes-type virus.

comatose. Platelet count decreased to 81,000 on the next day, and evidence of diffuse intravascular coagulopathy and bleeding at several sites occurred. Despite transfusion of blood components, bleeding and hypotension persisted. The patient died on day 14.

Autopsy did not reveal a major source of infection. The most significant findings were diffuse hepatic necrosis with ascites and bilateral pleural effusions. Light microscopy of the liver revealed hyaline and intranuclear inclusions that were brightly eosinophilic. The intranuclear inclusions were consistent with herpes viral infection.

Accordingly, formalin-fixed hepatic tissue was cut into small cubes of less than 1 mm to a side. The cubes were fixed in 2% osmium tetroxide, embedded in epoxy resin, and sectioned. The sections were stained with uranyl acetate and lead citrate and were examined in a JEOL 100-S microscope at an accelerating voltage of 70 kvs. The resulting electron micrographs showed viral particles having morphological characteristics consistent with herpes virus (Fig. 1). Immunoperoxidase staining of liver sections suggested type I herpes virus.

## Discussion

Before the postmortem discovery of herpes virus invasion of the liver, we considered the possibility that isoflurane had contributed to the development of hepatic necrosis in this patient. Many of the supposed features of "halothane hepatitis" were present: fever, anorexia, vomiting, and the development of liver dysfunction soon after anesthesia in a patient whose preoperative serum transaminases were normal. Absent as supporting features were previous exposure to a halogenated anesthetic, atopy, eosinophilia, rash, chills, and jaundice.

We believe this is the first report of herpes-virus-induced necrosis of the liver after anesthesia with isoflurane. Our patient was similar in several ways to a patient given enflurane anesthesia who subsequently had massive hepatic necrosis secondary to invasion of the liver by herpes virus (1). Both patients underwent long, intraabdominal procedures with initially uneventful postoperative courses. Both had signs of severe gastroenteritis with vomiting and diarrhea in association with high temperatures. Neither patient had eosinophilia or became jaundiced despite severe hepatic injury.

One difference between our patient and the patient given enflurane is that the latter patient had also been given chemotherapy for Hodgkin's disease and thus might have had decreased immunocompetence. Our patient had no obvious reason for decreased immunocompetence. Indeed, his attending physicians noted the rarity of the occurrence of herpes hepatitis in a patient whose immunocompetence is not compromised.

We cannot say whether isoflurane affected our patient's ability to produce an immune response. At 0.2 MAC, isoflurane, enflurane, and halothane all inhibit replication of measles virus by 50% and thus might be thought to protect against viral infection (2). At anesthetizing or higher concentrations, isoflurane does not inhibit neutrophil function, whereas enflurane does (3). Neither isoflurane nor enflurane inhibits phagocytosis (4).

Our patient also received nitrous oxide. Unlike isoflurane, nitrous oxide inactivates methionine synthetase in the livers of mice (5) and humans (6). Inactivation of methionine synthetase by nitrous oxide impairs the formation of DNA in humans (7). Prolonged administration of nitrous oxide to humans can markedly decrease plasma levels of neutrophils and platelets, and death from sepsis may result (8). Shorter periods of exposure produce similar but more subtle changes in neutrophils (9).

The effect of nitrous oxide on white cell function is unclear. Cullen (10) found no effect of 30 min of 80% nitrous oxide on in vitro phagocytosis by human leukocytes. On the other hand, Nunn and O'Morain (11) found that nitrous oxide inhibited neutrophil motility and chemotaxis whereas halothane did not. Moudgil et al. (12) also found that nitrous oxide inhibited neutrophil (and monocyte) chemotaxis, but isoflurane did not. The results of these in vitro studies appear to differ from those conducted on leukocytes from surgical patients exposed to nitrous oxide: such exposure appears to increase random migration (13) and chemotaxis (14). Finally, the in vitro ability of lymphocytes (from patients with cancer) to kill tumor cells appears to be decreased after such patients have been given nitrous oxide (15,16).

In summary, we describe a patient who had massive hepatic necrosis after anesthesia with isoflurane and nitrous oxide. Invasion of the liver by herpes virus was the immediate cause of injury to the liver. Whether isoflurane or nitrous oxide contributed to a decrease in immunocompetence and thus increased vulnerability to viral attack remains unknown; however, the rarity of such reports suggests that immunocompetence remains adequate in the vast majority of patients given isoflurane and nitrous oxide.

## References

1. Douglas HJ, Eger EI II, Biava CG, Renzi C. Hepatic necrosis associated with viral infection after enflurane anesthesia. N Engl J Med 1977;296:553–5.
2. Knight PR, Nahrwold ML, Bedows E. Inhibiting effects of enflurane and isoflurane anesthesia on measles virus replication: comparison with halothane. Antimicrob Agents Chemother 1981;20:298–306.
3. Welch WD. Effect of enflurane, isoflurane, and nitrous oxide on the microbicidal activity of human polymorphonuclear leukocytes. Anesthesiology 1984;61:188–92.
4. Mathieu A, Mathieu D, Stinnett JD, Alexander JW. Effect of three halogenated volatile anesthetics on human leukocyte phagocytic and microbicidal functions. Anesthesiology 1983;59:A294.
5. Koblin DD, Watson JE, Deady JE, Stokstad ELR, Eger EI II. Inactivation of methionine synthetase by nitrous oxide in mice. Anesthesiology 1981;54:318–24.
6. Koblin DD, Waskell L, Watson JE, Stokstad ELR, Eger EI II. Nitrous oxide inactivates methionine synthetase in human liver. Anesth Analg 1982;61:75–8.
7. Amess JAL, Burman JF, Rees GM, Nancekievill DG, Mollin DL. Megaloblastic haemopoiesis in patients receiving nitrous oxide. Lancet 1978;2:339–42.
8. Lassen HCA, Henriksen E, Neukirch F, Kristensen HS. Treatment of tetanus: severe bone-marrow depression after prolonged nitrous-oxide anaesthesia. Lancet 1956;1:527–30.
9. Skacel PO, Hewlett AM, Lewis JD, Lumb M, Nunn JF, Chanarin I. Studies on the haemopoietic toxicity of nitrous oxide in man. Br J Haematol 1983;53:189–200.
10. Cullen BF. The effect of halothane and nitrous oxide on phagocytosis and human leukocyte metabolism. Anesth Analg 1974;53:531–6.
11. Nunn JF, O'Morain C. Nitrous oxide decreased motility of human neutrophils in vitro. Anesthesiology 1982;56:45–8.
12. Moudgil GC, Forrest JB, Gordon J. The effect of volatile anaesthetics and nitrous oxide on human leukocyte chemotaxis in vitro. Canad Anaesth Soc J 1984;31:631–7.
13. Hill GE, Stanley TH, Lunn JK, Liu WS, English JB, Loeser EA, Kawamura R, Sentker CR, Hill HR. Neutrophil chemotaxis during halothane and halothane-$N_2O$ anesthesia in man. Anesth Analg 1977;56:696–702.
14. Hill GE, English JB, Stanley TH, Kawamura R, Loeser EA, Hill HR. Nitrous oxide and neutrophil chemotaxis in man. Br J Anaesth 1978;50:555–8.
15. Kumar S, Taylor G. Effect of surgery on lymphocytotoxicity against tumour cells. Lancet 1974;2:1564–5.
16. Vose BM, Moudgil GC. Effect of surgery on tumour-directed leucocyte responses. Br Med J 1975;1:56–8.

1134 ANESTH ANALG
1985;64:1134–6

# Loss of Radial Artery Pressure Trace During Internal Mammary Artery Dissection for Coronary Artery Bypass Graft Surgery

John B. Kinzer, MD, Peter R. Lichtenthal, MD, and Leonard D. Wade, MS

Coronary artery bypass graft (CABG) surgery for the treatment of ischemic heart disease was introduced in 1967 and has since become one of the most widely performed surgical procedures. Grafting has been performed using either autologous veins (generally the saphenous) or arteries (generally the internal mammary). In both early and long-term comparative studies (1–5), patency rates of internal mammary artery (IMA) grafts are clearly better than saphenous vein grafts. These recently reported results have led to increased use of IMA grafts for CABG surgery at our institution. However, we have encountered a recurring monitoring problem that is related not to equipment malfunction but rather to distortion of normal anatomy. We describe a case in which we lost the capability to monitor systemic blood pressure via the radial artery during IMA dissection.

## Case Report

A 67-yr-old, 76-kg man was scheduled for a two-vessel coronary artery bypass graft procedure with the use of the left internal mammary artery. Past medical history included an inferior wall myocardial infarction 24 months prior to admission, angina pectoris over the past year, and non-insulin-dependent diabetes mellitus over the past 10 yr. Previous surgery consisted of a cataract extraction under local anesthesia without complications. Medications included nifedipine, nadolol, and tolbutamide. He denied any drug allergies. His alcohol consumption was minimal, and he had stopped smoking 16 yr before. His physical examination was unremarkable. Allen's test revealed good bilateral ulnar arterial collateral flow. Preoperative laboratory values were within normal limits.

The patient was premedicated with scopolamine, 0.4 mg, and morphine sulfate, 10 mg, intramuscularly 2 hr before surgery started. He arrived in the operating room well sedated. A blood pressure cuff was placed on the left arm, and pressures were recorded. A 20-g catheter was inserted percutaneously into the left radial artery at the wrist with no difficulty. A pulmonary artery catheter was placed via the right internal jugular vein. Catheters were utilized for invasive monitoring of pressure and for obtaining blood samples. Before induction of anesthesia, both arms were placed at the patient's sides with no change in the blood pressure tracing. After preoxygenation, anesthesia was then induced with 10 mg intravenous diazepam. Atraumatic endotracheal intubation was facilitated with intravenous pancuronium and lidocaine. Anesthesia was maintained with halothane in oxygen–air.

A Favaloro self-retaining sternal retractor was used to lift the left side of the chest wall for better exposure of the internal mammary artery. After application of the retractor and during the dissection of the IMA, the systemic blood pressure waveform became more and more damped, until finally it appeared to be completely damped (Fig. 1). Suspecting that a mechanical problem caused catheter occlusion, we attempted to flush the arterial catheter. To our surprise, the catheter flushed without difficulty and blood could be aspirated with ease. However, the waveform still did not improve. Repositioning of the patient's left hand and checking the transducer produced no change in the waveform. We were unable to hear Korotkoff sounds using a blood pressure cuff on the left arm. After switching the cuff to the right arm, we were able to obtain blood pressure measurements. Throughout the episode, a normal pulmonary artery trace was evident and remained unchanged, suggesting that the patient's hemodynamic conditions were not deteriorating. With eventual release of the sternal retractor, an apparently normal pulsatile left radial artery pressure trace promptly returned (Fig. 2). Although the pressure was low, it responded immediately to fluid challenge. The remainder of the

---

Received from the Department of Anesthesia, Northwestern University Medical School, Chicago, Illinois. Accepted for publication May 17, 1985.

Address correspondence to Dr. Lichtenthal, Department of Anesthesia, Northwestern University Medical School, 303 East Superior Street, Chicago, IL 60611.

© 1985 by the International Anesthesia Research Society

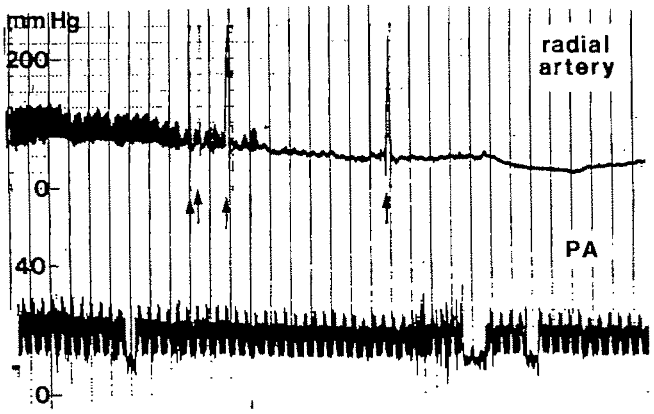


Figure 1. Slow-speed tracing of left radial artery pressure and pulmonary artery pressure. Notice that the radial artery pressure slowly decreases. Arrows denote periods of flushing and aspirating the radial artery catheter (paper speed, 0.25 mm/sec).

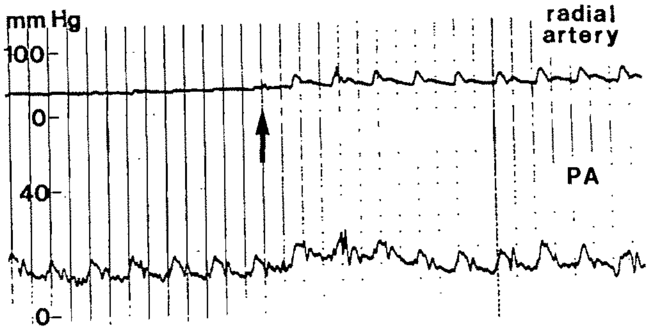


Figure 2. Normal-speed tracing of left radial pressure and pulmonary artery pressure. Arrow indicates the release of the retractor (paper speed, 25 mm/sec).

intraoperative course was uneventful, and there was no evidence of neural or vascular injuries postoperatively.

## Discussion

Past experience has shown that problems with measuring blood pressure can often be traced to the measuring system. A large number of these problems are mechanical in nature, such as catheter occlusion due to kinking or thrombus formation, improper connections, and air bubbles in the fluid-filled tubing/transducer system (6,7). On occasion, problems also arise from electronic failure of transducers or amplifiers (8). Unfortunately, we also must consider user errors caused by careless mistakes or inadequate operating knowledge of the equipment being used (9). While the pool for potential technical problems in measurement of blood pressure is large, the possibility cannot be overlooked that the equipment is indeed functioning properly, and a blood pressure appearing abnormal and inaccurate may, in fact, be abnormal and accurate. As new techniques and procedures are implemented during surgery, we must always be alert to how these new techniques affect the patient and our normal monitoring scheme.

We report a case in which the chest retraction necessary for IMA dissection produced erroneous pressure readings and eventually total loss of our ability to monitor systemic arterial pressure invasively. Since then, this problem has occurred numerous times with other patients at our institution. The usual methods for correcting a "dampened" waveform (e.g., flushing of the arterial cannula, aspiration of blood, positional changes of the cannula, transducer errors) did not resolve the problem for any of the cases. Also, importantly, a cuff blood pressure was unobtainable on the side on which the IMA dissection was being performed. The failure of all these methods indicates that all aspects of the monitoring system were functioning properly. The pressure trace returned only with the removal of the chest wall retractor, which reestablished adequate flow to the left extremity.

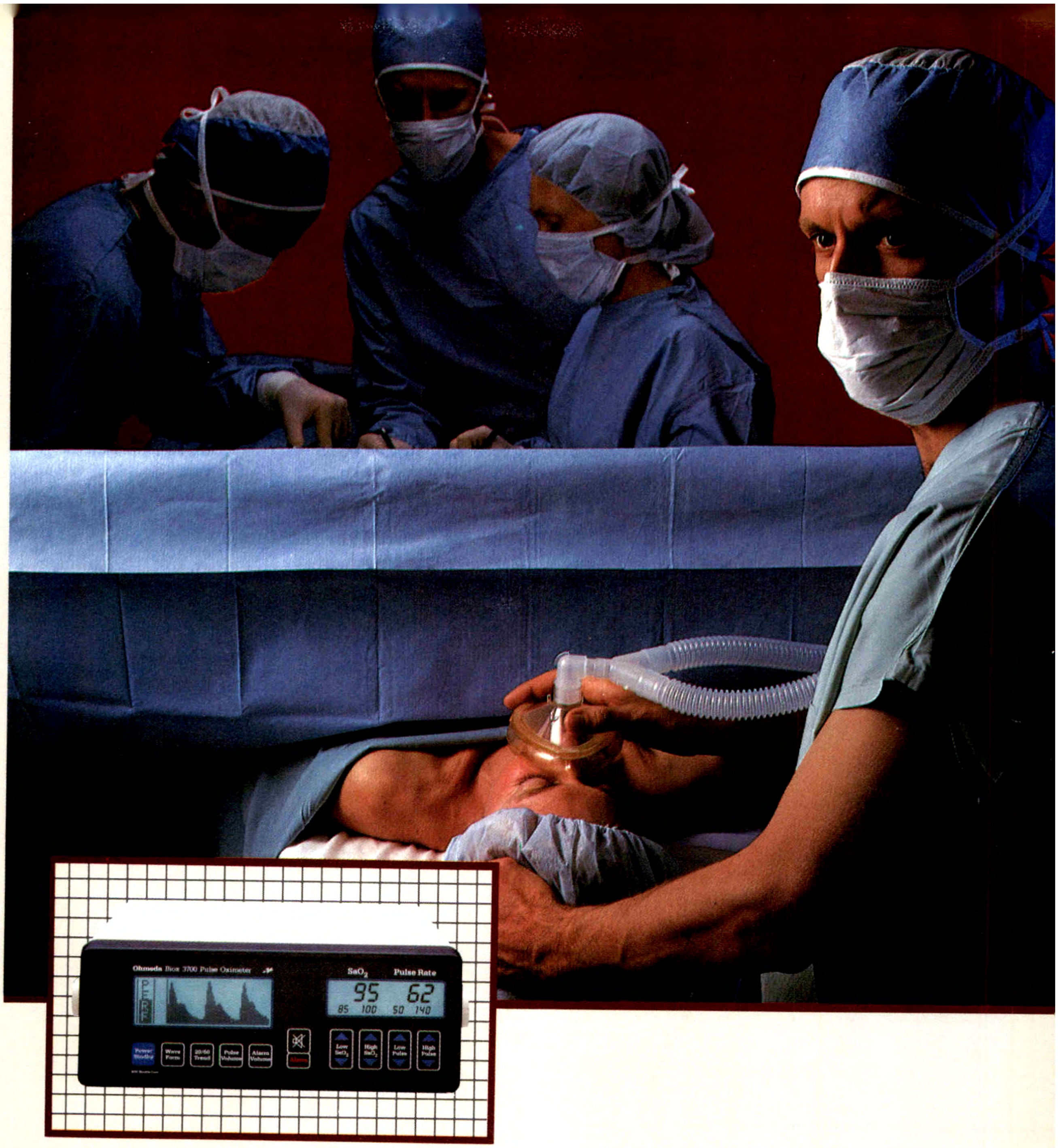
Because the origin of the IMA is from the proximal portion of the subclavian artery, the retraction and dissection of the IMA probably caused tension to develop at the juncture within the subclavian artery. This would decrease blood flow through the subclavian artery with subsequent loss of the radial artery pressure trace. This diminished blood flow also would account for the inability to auscultate a cuff blood pressure from that arm, because of the decreased or absent Korotkoff sounds.

Although utilization of the IMA for CABG surgery is not new in a chronological sense, it was definitely a new procedure to us and possibly to other institutions where saphenous vein grafts were usually used. A similar incident of erroneous pressure readings caused by retraction of the chest during IMA dissection was reported in 1976 (10). Since that time, use of the IMA graft for CABG surgery had lost popularity while saphenous vein grafts became more and more commonplace. The recently reported favorable results with IMA graft patency has caused cardiac surgeons to use this technique once again. Consequently, an old procedure suddenly has been transformed into a new procedure for many of us. Anesthesiologists must be prepared to cope with the potential problems accompanying this procedure.

We recommend that if the IMA is to be used for coronary artery bypass grafting, the radial artery cannula be placed on the contralateral extremity in order to assure adequate blood pressure monitoring.

## References

1. Loop FD, Irrarrazaval MJ, Bredec JJ, Siegel W, Taylor PC, Sheldon WC. Internal mammary artery graft for ischemic heart disease. Effect of revascularization on clinical status and survival. Am J Cardiol 1977;39:516–22.
2. Lytle BW, Loop RD, Thuris RL, Groves LK, Taylor, PC, Cosgrove DM. Isolated left anterior descending coronary atherosclerosis. Long-term comparison of internal mammary artery and venous autografts. Circulation 1980;61:869–74.
3. Lytle BW, Loop FD, Cosgrove DM, Easley K, Taylor PC. Long-term (5–12 years) sequential studies of internal mammary artery and saphenous vein coronary bypass grafts. Circulation 1983;68 (suppl. 3):114.
4. Okies JE, Page US, Bigelow JC, Krause AH, Salomon NW. The left internal mammary artery. The graft of choice. Circulation 1983;68 (suppl. 3):21.
5. Singh RN, Sosa JA, Green GE. Long-term fate of the internal mammary artery and saphenous vein grafts. J Thorac Cardiovasc Surg 1983;86:359–63.
6. Sisko F, Flagerdahl M, Neufeld GR. Artifactual hypotension without damping, a hazard of disposable diaphragm domes. Anesthesiology 1979;51:263–4.
7. Gardner RM. Direct blood pressure measurement—dynamic response requirements. Anesthesiology 1981;54:227–36.
8. Barbieri LT, Kaplan JA. Artifactual hypotension secondary to intraoperative transducer failure. Anesthesiology 1983;62:112–4.
9. Cooper JB, Newbower RS, Kitz RJ. An analysis of major errors and equipment failures in anesthesia management: considerations for prevention and detection. Anesthesiology 1984; 60:34–42.
10. Daimant M, Arkin DB. False radial-artery blood-pressure readings. Anesthesiology 1976;44:273.



# The **New** Ohmeda Biox 3700 Pulse Oximeter. Because hypoxemia is an $SaO_2$ problem.

**Why oximetry.**

A drop in arterial blood oxygenation ($SaO_2$) calls for quick and effective action. Especially in anesthesia, where oxygen starvation can jeopardize your patient's safety. Only oximetry provides the means for direct and efficient monitoring of $SaO_2$—giving you the crucial time needed to prevent clinical complications.

**Why Ohmeda.**

Now, the Ohmeda Biox 3700 Pulse Oximeter helps you in the prompt detection of hypoxemia. Continuous, reliable and non-invasive, only the 3700 shows you a plethysmographic waveform—plus $SaO_2$ trending of the past 20 or 60 minutes. Both visual and audible indicators continuously inform you of your patient's $SaO_2$ condition as you work. The 3700 has a battery backup, for easy transport and emergency power support. And its three types of probes make the 3700 ideally suited for any patient.

So, prevent minor procedures from becoming major hypoxic crises. Rely on the Ohmeda Biox 3700. It's the confident response to the critical demands of anesthesia.

**Ohmeda**

Ohmeda
4765 Walnut Street
Boulder, Colorado 80301 1 800 652 2469
A Division of The BOC Group, Inc.
**BOC Health Care**

# Anaquest

## introduces

# Enlon™

(edrophonium chloride
injection, USP)

**For faster reversal
of neuromuscular blockade
with fewer side effects**

**From the developers of
Ethrane® (enflurane) and Forane® (isoflurane)**

Anaquest
2005 West Beltline Highway
Madison WI 53713 2318
608 273 0019 800 ANA DRUG
A Division of BOC Inc

**BOC Health Care**

© 1985 BOC Inc

# 60-second reversal of neuromuscular blockade

- **Onset of reversal significantly faster than with neostigmine or pyridostigmine**—60 seconds versus 7 minutes for neostigmine, 12 minutes for pyridostigmine.[1,2]
- **Duration of reversal comparable to that of neostigmine**—66 minutes versus 76 minutes for neostigmine.[1,2*]
- **Significantly fewer muscarinic side effects and lower atropine requirement than with neostigmine**—edrophonium, 0.5 mg/kg, with only 7 $\mu$g/kg atropine, produced minimal change in heart rate or mean arterial pressure compared to noticeable changes in both indexes following neostigmine, 0.04 mg/kg, using *twice* the atropine dose (15 $\mu$g/kg).[1,2]
- **May be the reversal agent of choice for atracurium and vecuronium** "...compared with neostigmine, edrophonium has a more complete spectrum of atracurium reversal characteristics, and...antagonizes more rapidly residual atracurium-induced neuromuscular blockade."[3]

  "Edrophonium may in fact be the preferred reversal agent for routine use with [vecuronium], having the advantages that restoration of voluntary muscle function is very rapid, and that the relatively small dose of atropine required minimizes the unwanted side-effects of this drug."[4]

***Note:** When duration of action is adjusted for differences in onset of action, the relative durations are 65 minutes for edrophonium and 69 minutes for neostigmine.

1. Cronnelly R, Morris RB, Miller RD: Edrophonium: duration of action and atropine requirement in humans during halothane anesthesia. Anesthesiology 57:261-266, 1982. 2. Miller RD, et al: Comparative times to peak effect and duration of action of neostigmine and pyridostigmine. Anesthesiology 41:27-33, 1974. 3. Jones RM, Pearce AC, Williams JP: Recovery characteristics following antagonism of atracurium with neostigmine or edrophonium. Br J Anaesth 56:453-457, 1984. 4. Baird WLM, Bowman WC, Kerr WJ: Some actions of ORG NC45 and of edrophonium in the anaesthetized cat and in man. Br J Anaesth 54:375-385, 1982.

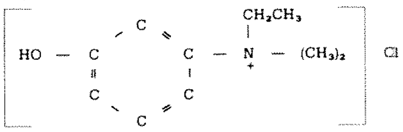
Please see use information on next page.

# Anaquest

# introduces
# Enlon™ (edrophonium chloride injection, USP)
# 60-second reversal of neuromuscular blockade

## DESCRIPTION

ENLON (edrophonium chloride injection, USP) is a rapid acting cholinergic (cholinesterase inhibitor). Chemically edrophonium chloride is ethyl (m-hydroxyphenyl) dimethylammonium chloride and its structural formula is:



ENLON contains in each mL of sterile solution:

(vial) 10 mg edrophonium chloride compounded with 0.45% phenol and 0.2% sodium sulfite as preservative, buffered with sodium citrate and citric acid. Its pH is adjusted to approximately 5.4

## CLINICAL PHARMACOLOGY

ENLON (edrophonium chloride injection, USP) activates neuromuscular transmission primarily by inhibiting or inactivating acetylcholinesterase. By inactivating the acetylcholinesterase enzyme, acetylcholine is not hydrolyzed by acetylcholinesterase and is thereby allowed to accumulate. The accumulation of acetylcholine at the sites of cholinergic transmission facilitates transmission of impulses across the myoneural junction.

## INDICATIONS AND USAGE

ENLON (edrophonium chloride injection, USP) is recommended as a reversal agent or antagonist of nondepolarizing muscle relaxants such as tubocurarine, metocurine, atracurium, vecuronium, or pancuronium. It is not effective against depolarizing relaxants such as succinylcholine and decamethonium. It is also useful if used adjunctively in the treatment of respiratory depression caused by curare overdosage. ENLON is recommended for use in the differential diagnosis of myasthenia gravis. It may also be used as an adjunct to evaluate treatment requirements of the disease, and for evaluating emergency treatment in myasthenic crisis. It is not recommended for maintenance therapy in myasthenia gravis.

## CONTRAINDICATIONS

ENLON (edrophonium chloride injection, USP) is not to be used in patients with known hypersensitivity to anticholinesterase agents, or in patients having urinary obstructions of mechanical type.

## WARNINGS

It is recommended that 1 mg atropine sulfate should be made available for immediate use, to counteract any severe cholinergic reaction. ENLON (edrophonium chloride injection, USP) should be used with caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Isolated instances of cardiac and respiratory arrest following administration of edrophonium chloride have been reported. It is postulated that these are vagotonic effects.

## PRECAUTIONS

**General:** As with any antagonist of nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance. Should a patient develop "anticholinesterase insensitivity" for brief or prolonged periods, the patient should be carefully monitored and the dosage of anticholinesterase drugs reduced or withheld until the patient again becomes sensitive to them.

**Drug Interactions:** The drug should not be administered prior to the administration of any nondepolarizing muscle relaxants. The drug should be administered with caution to patients with symptoms of myasthenic weakness who are also on anticholinesterase drugs. Anticholinesterase overdosage (cholinergic crisis) symptoms may mimic underdosage (myasthenic weakness) so the use of this drug may worsen the condition of these patients (see OVERDOSAGE section for treatment).

**Pregnancy Category C:** It is not known whether ENLON (edrophonium chloride injection, USP) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity, since there have been no adequate and well controlled studies in humans.

**Labor and Delivery:** The effect of ENLON on the mother and fetus, on the duration of labor or delivery, on the possibility that forceps delivery or other intervention or resuscitation of the newborn will be necessary is not known. The effect of the drug on the later growth, development and functional maturation of the child is also unknown.

**Nursing Mothers:** The safety of ENLON during lactation in humans has not been established.

## ADVERSE REACTIONS

A patient in myasthenic crisis, being treated with ENLON (edrophonium chloride injection, USP) should be observed for bradycardia or cardiac standstill and cholinergic reactions if an overdosage is given. Reactions common to anticholinesterase agents such as edrophonium chloride are:

**Cardiovascular:** arrhythmias (especially bradycardia), fall in output leading to hypotension;

**Respiratory:** increased tracheobronchial secretions, laryngospasm, bronchiolar constriction and respiratory muscle paralysis;

**Neurologic:** convulsions, dysarthria, dysphonia, and dysphagia;

**Gastrointestinal:** nausea, vomiting, increased peristalsis, increased gastric and intestinal secretions, diarrhea, abdominal cramps;

**Musculoskeletal:** weakness and fasciculations;

**Miscellaneous:** increased urinary frequency, diaphoresis, increased lacrimation, pupillary constriction, diplopia, and conjunctival hyperemia.

## OVERDOSAGE

Muscarine-like symptoms (nausea, vomiting, diarrhea, sweating, increased bronchial and salivary secretions and bradycardia) may appear with overdosage (cholinergic crisis) of ENLON (edrophonium chloride injection, USP) but may be managed by the use of atropine. Obstruction of the airway by bronchial secretions can arise and may be managed with suction (especially if tracheostomy has been performed) and by the use of atropine. Signs of atropine overdosage such as dry mouth, flush and tachycardia should be avoided as tenacious secretions and bronchial plugs may form. Should edrophonium chloride overdosage occur:

1. Maintain respiratory exchange.
2. Monitor cardiac function.

Appropriate measures should be taken if convulsions or shock are present.

## DOSAGE AND ADMINISTRATION

**The recommended adult intravenous injection for antagonism of neuromuscular block:**

Administer 1 mL (10 mg) slowly within a period of 30 to 45 seconds, the dosage may be repeated to a maximum total dose of 4 mL (40 mg). Its onset of action is manifest within 30 to 60 seconds after injection. Response should be monitored carefully and assisted ventilation should always be employed. When given to counteract muscle relaxant overdosage, the dose effect on respiration should be observed prior to repeat dosages and assisted ventilation should be employed.

**ENLON (edrophonium chloride injection, USP) Test in Differential Diagnosis of Myasthenia Gravis:**

**Adults:**

**Intravenous Dosage:** Prepare a tuberculin syringe with 1 mL (10 mg) of ENLON and an intravenous needle; intravenously inject 0.2 mL (2 mg) within 15 to 30 seconds. The needle should be left in situ. If a cholinergic reaction (muscarinic side effects, skeletal muscle fasciculations and increased muscle weakness) occurs, discontinue test and intravenously administer 0.4 mg to 0.5 mg atropine sulfate. Inject the remaining 0.8 mL (8 mg) only if no reaction occurs after 45 seconds. The test may be repeated after one-half hour.

**Intramuscular Dosage:** Intramuscularly inject 1 mL (10 mg) of ENLON. If hyperreactivity (cholinergic reaction) is demonstrated, retest the patient after one-half hour with another intramuscular injection of 0.2 mL (2 mg) ENLON. This will eliminate the possibility of false-negative reactions.

**Children:**

**Intravenous dose in children weighing up to 75 pounds:**

Intravenously inject 0.1 mL (1 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 0.5 mL (5 mg). The recommended dose in infants is 0.05 mL (0.5 mg).

**Intravenous dose in children weighing above 75 pounds:**

Intravenously inject 0.2 mL (2 mg) ENLON. If there is no response within 45 seconds, incremental doses of 0.1 mL (1 mg) given every 30 to 45 seconds may be administered to a maximum total dose of 1 mL (10 mg).

**Intramuscular Dose:** Intramuscularly inject 0.2 mL (2 mg) ENLON in children weighing up to 75 pounds; above this weight, the dose is 0.5 mL (5 mg). All signs of hyperreactivity (cholinergic reaction) noted in the intravenous test will be demonstrated in the intramuscular test; however, there is a two to ten minute delay before reaction.

**ENLON (edrophonium chloride injection, USP) Test to Evaluate Treatment Requirements in Myasthenia Gravis:**

The test dose of ENLON should follow one hour after oral intake of the drug being used to treat the disease. The recommended dose is 0.1 mL to 0.2 mL (1 mg to 2 mg) administered intravenously. Response to ENLON test dose in treated myasthenic patients is summarized as follows:

**Undertreated patient:** Myasthenic response; characterized by increased muscle strength (ptosis, diplopia, dysphonia, dysphagia, dysarthria, respiration, limb strength). This indicates inadequate treatment of the myasthenic condition.

**Controlled patient:** Adequate response; characterized by no change in muscle strength with minimal side reactions (lacrimation, diaphoresis, salivation, abdominal cramps, nausea, vomiting, diarrhea). Fasciculations (orbicularis oculi, facial muscles, limb muscles) may or may not occur. The response indicates that therapy is stabilized.

**Overtreated patient:** Cholinergic response; characterized by decreased muscle strength and severe side reactions. Fasciculations may be observed. This response occurs in myasthenics who have been overtreated with anticholinesterase drugs.

**ENLON (edrophonium chloride injection, USP) Test in Crisis:**

Crisis in the myasthenic patient is characterized as a state of severe respiratory distress with inadequate ventilatory exchange, and unpredictable response to medication. If the patient is apneic, achieve ventilatory exchange immediately to avoid cardiac arrest and irreversible central nervous system damage.

The ENLON Test should not be conducted until respiratory exchange is maintained. The cholinergic patient will exhibit further weakness in the muscles of respiration and will have increased oropharyngeal secretions if ENLON is administered. Whereas, upon administration of ENLON the myasthenic patient will demonstrate improved respiration and can be given additional medication. To perform the test prepare a syringe with 0.2 mL (2 mg) ENLON and intravenously inject 0.1 mL (1 mg). The patient's cardiac and respiratory actions should be observed for change. The remaining 0.1 mL (1 mg) may be injected after one minute if no response is noted. If, after the entire 0.2 mL (2 mg) dose has been injected, no improvement in respiration occurs, discontinue all anticholinesterase drugs. Controlled ventilation can be achieved by tracheostomy with assisted respiration.

## HOW SUPPLIED

ENLON (edrophonium chloride injection, USP):

**NDC** 10019-873-15 15 mL multidose vials. 2-85

# Anesthesia and Analgesia

## BACK ISSUES AVAILABLE

Available at $3.00 per Issue

| Vol. | Year | Numbers Available | | | | | | Vol. | Year | Numbers Available | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 33 | 1954 | – | 2 | 3 | 4 | 5 | 6 | 41 | 1962 | – | 2 | 3 | – | 5 | 6 |
| 34 | 1955 | 1 | 2 | 3 | 4 | 5 | 6 | 42 | 1963 | – | – | 3 | 4 | 5 | 6 |
| 35 | 1956 | 1 | 2 | 3 | – | 5 | 6 | 43 | 1964 | 1 | – | 3 | – | 5 | 6 |
| 36 | 1957 | – | – | – | – | – | 6 | 44 | 1965 | 1 | 2 | 3 | 4 | 5 | 6 |
| 37 | 1958 | 1 | 2 | 3 | 4 | 5 | 6 | 45 | 1966 | – | 2 | – | 4 | 5 | 6 |
| 38 | 1959 | – | 2 | 3 | 4 | – | 6 | 46 | 1967 | – | 2 | 3 | 4 | – | 6 |
| 39 | 1960 | – | – | 3 | 4 | 5 | 6 | 47 | 1968 | – | – | 3 | 4 | 5 | 6 |
| 40 | 1961 | – | – | – | 4 | 5 | 6 | 48 | 1969 | 1 | 2 | 3 | – | 5 | – |

Available at $4.50 per Issue

| Vol. | Year | Numbers Available | | | | | | Vol. | Year | Numbers Available | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 49 | 1970 | 1 | – | – | – | 5 | 6 | 54 | 1975 | – | 2 | 3 | – | – | 6 |
| 50 | 1971 | 1 | 2 | – | – | – | – | 55 | 1976 | – | 2 | 3 | 4 | 5 | 6 |
| 51 | 1972 | – | 2 | 3 | – | – | 6 | 56 | 1977 | 1 | 2 | 3 | 4 | 5 | 6 |
| 52 | 1973 | 1 | 2 | 3 | 4 | 5 | 6 | 57 | 1978 | 1 | 2 | 3 | 4 | 5 | 6 |
| 53 | 1974 | – | 2 | 3 | 4 | – | – | | | | | | | | |

Available at $5.50 per Issue

| Vol. | Year | Numbers Available | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 58 | 1979 | 1 | 2 | 3 | 4 | 5 | 6 | (only six issues published) | | | | | |
| 59 | 1980 | – | – | 3 | 4 | 5 | 6 | – | 8 | 9 | 10 | 11 | 12 |
| 60 | 1981 | 1 | 2 | 3 | 4 | 5 | 6 | – | – | 9 | 10 | 11 | 12 |
| 61 | 1982 | 1 | 2 | 3 | 4 | 5 | 6 | – | – | 9 | 10 | 11 | 12 |

SINGLE ISSUES PRIOR TO 1954: Write to publisher at address below for listing of issues available at $2.00 each.

OTHER PUBLICATIONS AVAILABLE:
"Basic and Clinical Physiology of the Liver" (Supplement to Sept.–Oct. 1965 issue)—$3.00.
Ten-Year (1960–1969) Cumulative Index—$3.00.
Ten-Year (1970–1979) Cumulative Index—$3.00.
1982 (56th Congress) Review Course Lectures—$5.00.
1983 (57th Congress) Review Course Lectures—$5.00.
1984 (58th Congress) Review Course Lectures—$6.00.
1985 (59th Congress) Review Course Lectures—$6.00.

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, Ohio 44122

Please send me the publications circled above, or listed hereunder:

☐ Check for $________ enclosed.
☐ Please send bill with understanding that ordered material will be sent when payment is received.

Name ________________________________________

Address ________________________________________

City, State, Zip ________________________________________

Requests for single issues beginning with Vol. 62 should be sent to Elsevier Science Publishing Co, Inc., 52 Vanderbilt Avenue, New York, NY 10017.
Ten-Year Cumulative Index (1975–1984) is available only through Elsevier.

# THROUGHOUT THE PERI-

## to relieve excessive anxiety

### Rapid relief of anxiety and apprehension

Anxiety is an extremely common reaction to the stress of anesthesia and surgery. Often at its most acute stage in the minutes just before induction, anxiety may even affect the outcome of the surgical procedure.[1]

To relieve anxiety promptly and predictably, no agent is more effective than Injectable Valium® (diazepam/Roche) I.V.

Within minutes after an I.V. injection,[2,3] most patients become noticeably calmer, sedated yet easily aroused if necessary. This response is prompt and predictable—just the kind you want in the anxious moments before surgery.

**Rarely compromises cardiac or respiratory function** Injectable Valium rarely produces clinically significant alterations in basal circulatory parameters.[4-6] In a series of 16,000 patients, apnea occurred in only three patients given Injectable Valium intravenously.[7] However, caution should be taken when administering the agent to elderly or debilitated patients with limited pulmonary reserve. Resuscitative equipment should be available for all patients, and narcotics should be reduced by one-third or more; in some cases they may be eliminated.

Copyright © 1985
by Roche Products Inc.
All rights reserved.

# OPERATIVE PERIOD

## to diminish recall

**Diminishes recall of unpleasant or painful procedures** When patients have vivid memories of invasive procedures, they may be less than willing to undergo such procedures again, even if they are medically necessary.[8,9] Recall of procedures such as endotracheal intubation can be diminished by the rapid-acting amnesic effect of Injectable Valium (diazepam/Roche) I.V. Anterograde amnesia usually begins within three minutes after a single I.V. injection, peaks within ten minutes and lasts for 20 to 60 minutes.[3,10,11]

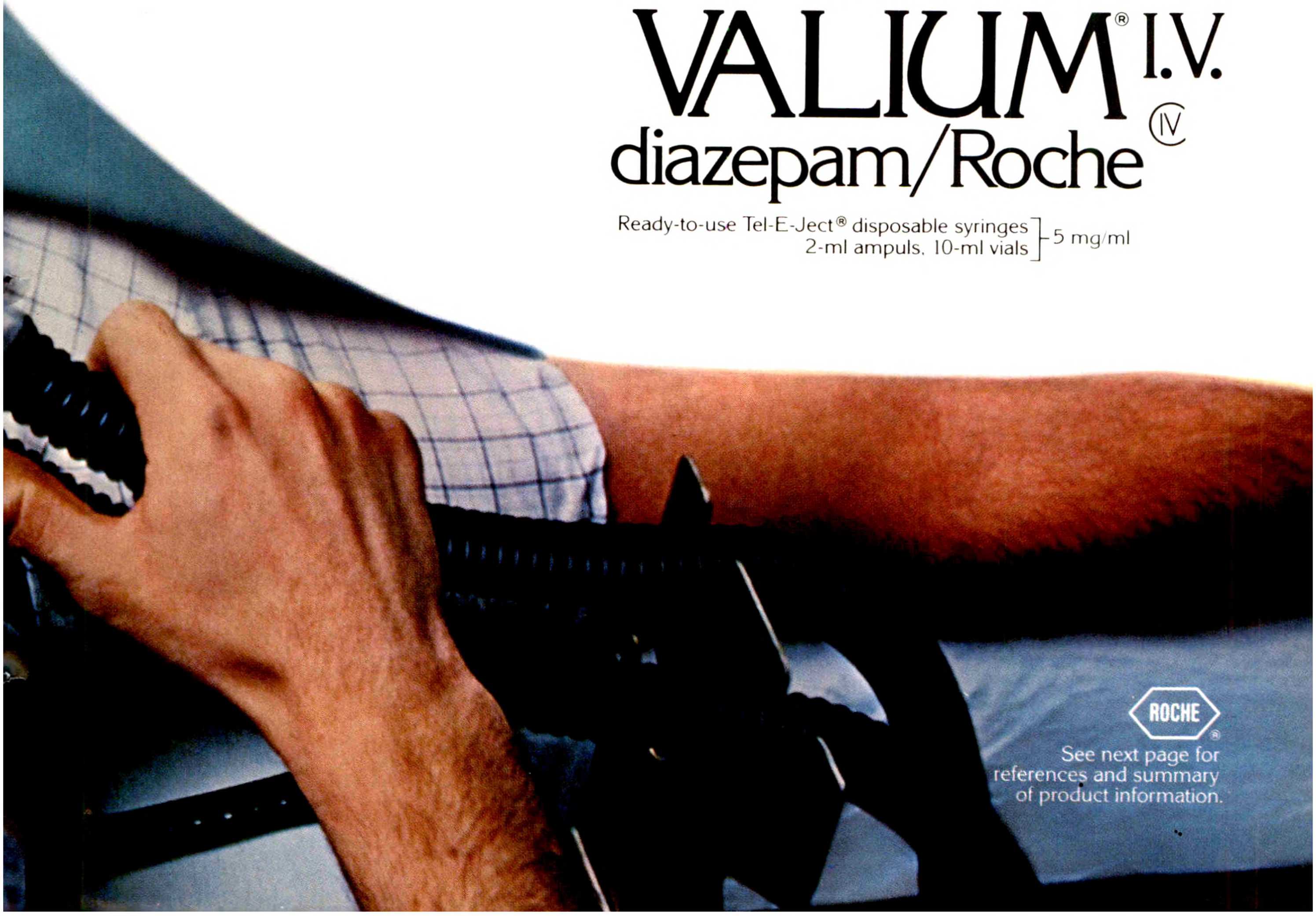
This predictable pattern of action distinguishes Injectable Valium from other agents that can produce amnesia and sedation. Other agents can take 15 to 30 minutes to achieve the desired effect, and the effects may last for 24 hours or more.[2] However, patients should be warned about driving or performing other potentially dangerous activities after receiving Injectable Valium.

**Easily titrated for desired effect** The compact 10-mg prefilled syringe makes individualized titration of Injectable Valium (diazepam/Roche) simple because there is convenient, easily readable milligram calibration on both sides of the barrel. And unlike other injectable agents, Injectable Valium needs no reconstitution before administration and no refrigeration during storage. Do not mix or dilute Valium with other drugs or solutions. Administer slowly in a large vein or through the infusion line as close to the vein insertion site as possible.

Injectable Valium. In a class by itself for rapidly relieving anxiety and diminishing recall.

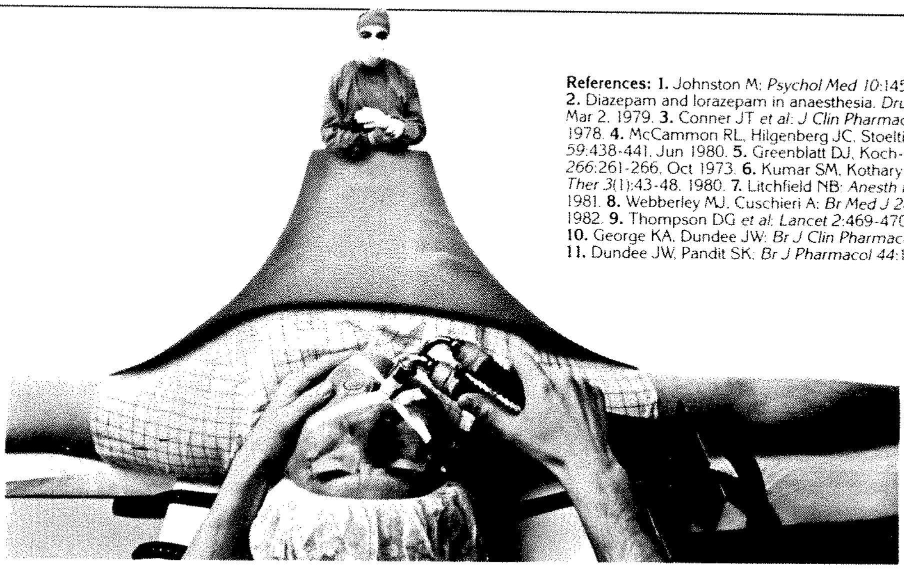
Prompt
Predictable
INJECTABLE
**VALIUM® I.V.**
ⓘⓥ
diazepam/Roche

Ready-to-use Tel-E-Ject® disposable syringes }
2-ml ampuls, 10-ml vials } 5 mg/ml



ROCHE®

See next page for references and summary of product information.



**References:** **1.** Johnston M: *Psychol Med 10*:145-152, Feb 1980. **2.** Diazepam and lorazepam in anaesthesia. *Drug Ther Bull 17*:19-20, Mar 2, 1979. **3.** Conner JT *et al*: *J Clin Pharmacol 18*:285-292, May-Jun 1978. **4.** McCammon RL, Hilgenberg JC, Stoelting RK: *Anesth Analg 59*:438-441, Jun 1980. **5.** Greenblatt DJ, Koch-Weser J: *Am J Med Sci 266*:261-266, Oct 1973. **6.** Kumar SM, Kothary SP, Zsigmond EK: *Clin Ther 3*(1):43-48, 1980. **7.** Litchfield NB: *Anesth Prog 29*:11-17, Jan-Feb, 1981. **8.** Webberley MJ, Cuschieri A: *Br Med J 285*:251-252, Jul 24, 1982. **9.** Thompson DG *et al*: *Lancet 2*:469-470, Aug 30, 1980. **10.** George KA, Dundee JW: *Br J Clin Pharmacol 4*:45-50, Feb 1977. **11.** Dundee JW, Pandit SK: *Br J Pharmacol 44*:140-144, Jan 1972.

# INJECTABLE VALIUM® (diazepam/Roche) Ⓒⅳ

**Please consult complete product information, a summary of which follows:**

**Indications:** Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; tetanus; status epilepticus, severe recurrent seizures; adjunctively in anxiety, tension or acute stress reactions prior to endoscopic/surgical procedures; cardioversion.

**Contraindications:** Hypersensitivity; acute narrow angle glaucoma; may be used in patients with open angle glaucoma receiving appropriate therapy.

**Warnings:** *To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling and, rarely, vascular impairment when used I.V.: inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins,* i.e., *dorsum of hand or wrist; use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*

Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest. concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea; have resuscitative facilities available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least 1/3, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status.

Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation after long use of excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after long, continuous use at high therapeutic levels. After extended therapy, gradually taper dosage.

> ***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations, as suggested in several studies. Consider possibility of pregnancy when instituting therapy: advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for OB use.

Efficacy/safety not established in neonates (age 30 days or less); prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence; can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.

**Precautions:** Although promptly controlled, seizures may return; readminister if necessary; not recommended for long-term maintenance therapy.

If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam/Roche), *i.e.*, phenothiazines, narcotics, barbiturates, MAO inhibitors, antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

**Adverse Reactions:** Drowsiness, fatigue, ataxia, venous thrombosis/phlebitis at injection site, confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo, constipation, nausea, incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat and chest have been reported in peroral endoscopic procedures. Isolated reports of neutropenia, jaundice; periodic blood counts, liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

**Dosage:** Usual initial dose in older children and adults is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.)

For dosages in infants and children see below; have resuscitative facilities available.

*I.M. use: by deep injection into the muscle.*

*I.V. use: inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins,* i.e., *dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*

Moderate anxiety disorders and symptoms of anxiety, 2 to 5 mg I.M. or I.V. and severe anxiety disorders and symptoms of anxiety, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcohol withdrawal, 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary. Muscle spasm, in adults, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); in children, *administer I.V. slowly;* for tetanus in infants over 30 days of age, 1 to 2 mg I.M. or I.V., repeat every 3 to 4 hours if necessary; in children 5 years or older, 5 to 10 mg repeated every 3 to 4 hours as needed. Respiratory assistance should be available.

Status epilepticus, severe recurrent convulsive seizures (I.V. route preferred), 5 to 10 mg adult dose administered slowly, repeat at 10- to 15-minute intervals up to 30 mg maximum. Repeat in 2 to 4 hours if necessary, keeping in mind possibility of residual active metabolites. Use caution in presence of chronic lung disease or unstable cardiovascular status. Infants (over 30 days) and children (under 5 years), 0.2 to 0.5 mg slowly every 2 to 5 min., up to 5 mg (I.V. preferred). Children 5 years plus, 1 mg every 2 to 5 min., up to 10 mg (slow I.V. preferred); repeat in 2 to 4 hours if needed. EEG monitoring may be helpful.

In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg I.V. within 5 to 10 minutes prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

**Management of Overdosage:** Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of limited value.

**Supplied:** Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1 and 10; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

ROCHE®
Manufactured by Hoffmann-La Roche Inc.
Nutley, New Jersey 07110
Distributed by Roche Products Inc.
Manati, Puerto Rico 00701

## 24th CLINICAL CONFERENCE IN PEDIATRIC ANESTHESIOLOGY

### JANUARY 24, 25, & 26, 1986

To Be Held At The:

Los Angeles Marriott Hotel

For Information Write To:

**Wayne Herbert, M.D.
Program Director
Pediatric Anesthesiology
Foundation
Childrens Hospital of
Los Angeles
P.O. Box 54700
Los Angeles, CA 90054**

---

## CALIFORNIA

Kern Medical Center, a UCLA affiliated teaching hospital located in Bakersfield, 105 miles north of Los Angeles, is recruiting a chairperson. Candidates must be Board Certified; have 5 years clinical experience; have experience in organized medical staff departmental tasks; and be qualified for an appropriate academic appointment.

KMC has 240 beds hospital; 16,000 annual admissions; 100,000 outpatient and 60,000 emergency visits; 3,600 obstetrical deliveries; and 5,000 surgical cases in a variety of specialties including trauma.

There is a competitive compensation package incorporating base salary, practice plan financial incentive, and outstanding benefits.

Send letter of inquiry with Curriculum Vitae to:

**Donald A. Lackey, M.D.
Medical Director
Chairman, Search Committee
Kern Medical Center
1830 Flower Street
Bakersfield, California 93305**

EO/AA Employer

---

## THE USE OF FIBEROPTIC ENDOSCOPES IN ANESTHESIA

### A Workshop Presented By The Department of Anesthesia, Northwestern University Medical School and Veterans Administration Lakeside Medical Center Chicago, Illinois

**DATES:** *Saturday, November 23, 1985;*
*Saturday, March 1, 1986;*
*Saturday, May 17, 1986*

**SPEAKERS:** *Drs. R. Braunschweig,*
*E. A. Brunner,*
*M. H. M. Dykes,*
*C. W. Joshi,*
*A. Koht, T. C. Krejcie,*
*E. Matthew, S. J. Yellich*

### Didactic Session

Application of flexible fiberoptic endoscopes in anesthesia and critical care; physical characteristics of flexible endoscopes; indications, contraindications and possible complications of fiberoptic endoscopy; key points to aid in teaching and learning various intubation techniques.

### Practical Session

1. Using a model of the Tracheobronchial tree, the participant will receive instruction concerning the proper handling of these instruments and through actual practice will improve the dexterity necessary for successful implementation. A special teaching station will enable each participant to use a flexible endoscope to aid in gaining optimum placement of a double-lumen endobronchial tube.
2. Supervised practice on intubation manikins will give each participant "hands-on" experience with various techniques for oral and nasal intubation. A special technique for intubation of the pediatric patient will be demonstrated with a subsequent practice session.

This course has been approved for 7 hours of credit in Category I of the Physician's Recognition award of the American Medical Association.

Registration will be limited to 50 participants. The fee is $225.

For information and application please contact:

**Ms. Paula Puntenney
Alumni Center for Continuing Education
Northwestern University Medical School
301 E. Chicago Ave.
Chicago, IL 60611
Telephone (312) 908-8533**

DINAMAP
Halothan
Vapor 19.1
Isoflurane
Vapor 19.1

# Setting the standard in hypoxemia monitoring.

# The Nellcor® N-100 pulse oximeter.

**Now, for patient safety in all cases... all the time.**

Leading clinicians in major medical centers use the Nellcor N-100 pulse oximeter. Over thirty-five published papers* document the need for this monitor.

By continuously monitoring arterial oxygen levels, the Nellcor N-100 can detect patient hypoxemia before it results in adverse outcome.

With each heartbeat, there is real-time, non-invasive measurement of arterial oxygen saturation, pulse rate, and pulse amplitude...

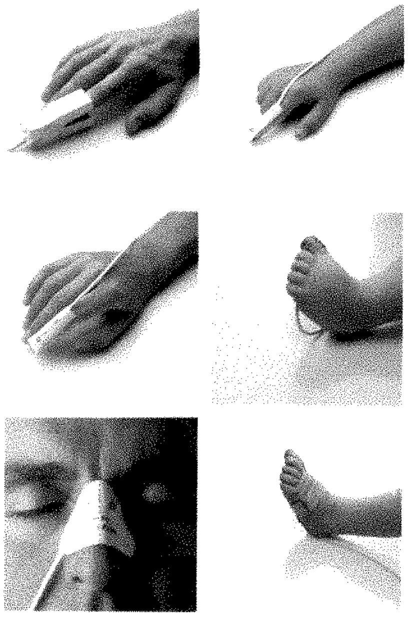
Information that is critical to your patient's well-being.

**Variable beep plus an alarm system for early warning and instant detection.**

The unique variable beep warns instantly if the patient's oxygen level changes. So corrective action can be taken immediately...before complications develop.

Plus, audible and visual alarms alert if saturation or pulse rate fall outside preset limits.

An unprecedented safety net.



**A complete family of sensors for a wide range of non-invasive oxygen monitoring needs.**

You can choose sensors in different sizes and configurations to monitor all patients—from neonates to adults.

Even in difficult cases such as low peripheral perfusion, active patients, and long-term care.

**Easy to use.**

Apply the sensor, switch on the monitor, and read the results.

There's no site preparation, no heater, and no need to move the sensor frequently.

For more information, write or call Nellcor toll-free at 800 433-1244. (In California, 800 351-9754)

The Nellcor N-100 pulse oximeter. Setting the standard in hypoxemia monitoring.

NELLCOR®

Nellcor Incorporated
25495 Whitesell Street
Hayward, California 94545
415 887-5858
Telex 172 428

*Bibliography on file at Nellcor Incorporated.

Nellcor is a registered trademark of Nellcor Incorporated.

KING SAUD UNIVERSITY
COLLEGE OF MEDICINE
RIYADH, SAUDI ARABIA

CARDIAC ANAESTHESIOLOGISTS

Applications are invited from suitably qualified anaesthesiologists to fill the posts of Consultants, Senior Registrars, and Registrars in the Cardiac Surgery Unit projected to open in June 1986, at King Khalid University Hospital.

Applicants should have American Board with two years experience in Cardiac Anaesthesia or other equivalent qualification.

Very attractive and negotiable salaries.

Application letter with comprehensive curriculum vitae and addresses of three references should be sent to:

The Dean, College of Medicine
King Saud University
P.O. Box 2925
Riyadh 11461, Saudi Arabia

---

**ANESTHESIOLOGISTS**

**St. Vincent Medical Center's Anesthesia Department** is expanding. We are seeking 2 board certified or board eligible anesthesiologists to join an 8 member BC/BE group with 15 CRNA's.

You will need 3 to 5 years experience with all types of anesthesia and intra-operative monitoring techniques.

**St. Vincent** is a 741-bed community teaching hospital with full surgical facilities, including neurological, open heart, retinal, vascular, obstetrical, plastic, as well as ambulatory outpatient surgery.

Located in one of Ohio's newest cities, Toledo boasts of spectacular waterfront developments, an art museum, symphony, theater and zoo rated among the top ten in the country, fine restaurants and shopping centers. In addition, year-round sports facilities are available along with spectator sports such as baseball and hockey.

For immediate consideration, please send your C.V. and a cover letter to: **Lynn Scott, Manager Recruitment Employment,**

St. Vincent Medical Center
**2213 Cherry St. • Toledo, OH 43608**
An Equal Opportunity Employer

---

**ANESTHESIOLOGISTS**

Major 850+ bed tertiary care teaching facility seeks qualified individuals or group to be part of a restructured Anesthesiology Service. Candidates must be Board Certified or Board eligible and qualify for academic appointment at our affiliated medical school. Attractive compensation arrangements. Please submit curriculum vitae to

**Robert K. Match, MD**
**President**

**LONG ISLAND JEWISH MEDICAL CENTER**

New Hyde Park, NY 11042
*an equal opportunity employer*

---

**ANESTHESIA STAFFING CRISIS**

CALL 1-800 FAST GAS (327-8427)
24 HOUR HOT LINE

WORLDWIDE ANESTHESIA ASSOCIATES, INC.

THE NATION'S LARGEST PROVIDER OF PROFESSIONAL ANESTHESIA PERSONNEL

ANESTHESIOLOGISTS • CERTIFIED REGISTERED NURSE ANESTHETISTS • EMERGENCY AND SCHEDULED RELIEF • LOCUM TENENS • CONTRACT MANAGEMENT • PERMANENT RECRUITING •

Worldwide Anesthesia Associates, Inc.

P.O. Box 1547 • UKIAH, CALIFORNIA 95482 • U.S.A.

# Classified Advertising

**ANESTHESIOLOGY FELLOW**

Two openings for 1-yr obstetrical anesthesia fellowship, one beginning January 1986 and the other, July 1986. Program includes 6 months each in the Departments of Anesthesiology at UCI Medical Center and Memorial Hospital Medical Center, Long Beach. Both are Level 3 Perinatal Centers with 4000 deliveries per year. there is opportunity to take part in clinical research and teaching of medical students. Applicants must be eligible for California state licensure. Inquiries from all qualified applicants are welcome. Contact Ho Joon Choi, MD, Director of Obstetric Anesthesia, University of California, Irvine Medical Center, 81A, Orange, CA 92668.

**ICU ANESTHESIOLOGIST**

Critical Care subspecialist needed to integrate with the Departments of Medicine, Surgery, and Neurosurgery for clinical care, resident teaching, and research. Must be board certified in anesthesiology and preferably also boarded in internal medicine or surgery. Excellent salary and outstanding benefits package. Please submit curriculum vitae to James E. Cottrell, MD, Professor and Chairman, 450 Clarkson Avenue, Box 6, Brooklyn, NY 11203. DMC #762, Equal opportunity/affirmative action employer SUNY-Downstate Medical Center.

**ANESTHESIOLOGISTS**

BC/BE to join progressive group of MDs and CRNAs encompassing all specialties in attractive Gulf Coast community. Excellent quality of life, friendly city with four-year colleges and abundant opportunities for sailing, fishing, water sports, and hunting. Candidates must be well-trained, enthusiastic, and personable. Experienced anesthesiologists and/or recent graduates are encouraged to apply. Please send CV with reply to Box K22, % *Anesthesia & Analgesia*, Desk Editorial, 52 Vanderbilt Avenue, New York, New York 10017.

**"ANESTHESIA, YOUR BABY, AND YOU"**

This obstetric anesthesia VIDEOTAPE can help you with patient education and informed consent, as well as nursing and student education. Contact: APPCOR PRODUCTIONS, 3652 Carleton St, San Diego, CA 92106.

**CENTRAL MARYLAND**

Opportunity for BC/BE anesthesiologists beginning January 1986. Good location. Corporate benefits. Minimal call. Send CV to Box G17A, % *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

**THE DEPARTMENT OF ANESTHESIOLOGY, ORAL ROBERTS UNIVERSITY SCHOOL OF MEDICINE**

currently has openings for Assistant/Associate Professor with interests in teaching, clinical practice and research. Excellent opportunity for board eligible/board certified physician in an institution dedicated to philosophy of Whole Person Medicine. Rank and salary commensurate with qualifications and negotiable. The City of Faith Medical and Research Center is a Christian ministry that employs without regard to race, color, sex, age, handicap, national origin or status as a veteran. Send CV and names of three references to James Mayhew, MD, Chairman, Department of Anesthesiology, Oral Roberts University School of Medicine, City of Faith Medical & Research Center, 8181 South Lewis, Tulsa, OK 74137-1270.

**NEW YORK: PEDIATRIC ANESTHESIOLOGIST**

Expanding Division of Pediatric Anesthesia, Department of Anesthesiology, Columbia University College of Physicians and Surgeons is seeking individuals with training in anesthesia and pediatrics. Division responsibilities are in the operating room and intensive care unit. Applicants should possess excellent clinical and teaching skills as well as research interests. Interested individuals should reply to **Peter Rothstein, MD, Director, Division of Pediatric Anesthesia, Box 62, Babies Hospital, 622 West 168th Street, New York, NY 10032.** Columbia University is an equal opportunity employer.

**NORTH CAROLINA**

Temporary and permanent BE/BC anesthesiologists needed to join fee-for-service group in small community in heart of Blue Ridge Mountains. Salary first year. Send inquiries and CV to Watauga Anesthesia Associates, PA, 301 Birch Street, Boone, NC 28607.

**TUTORING FOR WRITTEN AND ORAL BOARD EXAMS:**

Individual or small group sessions given in New York City, San Francisco, and Hawaii. Unique approach to development of test-taking skills, including mock orals. Basic science emphasis. Include phone number in response. Reply to Box K23, % *Anesthesia and Analgesia*, Desk Editorial, 52 Vanderbilt Avenue, New York, NY 10017.

**MDAS OR CRNAS: TRANS-AMERICAN ANESTHETISTS, WEST**

Temporary or Permanent MDAs, CRNAs, ready to serve you, up-to-date skills, cooperative, licensed, insured professionals caring about you. Call 1-800-762-1258, Box 24432, Colorado Springs, CO 80918, or 303-598-2788 (CO).

**UTAH**

The University of Utah seeks an anesthesiologist who is board certified in anesthesiology, preferably with a PhD in physiology or pharmacology for a position at the level of Assistant Professor. Candidates should be qualified in clinical care, have previous teaching experience, and be capable of independent basic science research. Send curriculum vitae to K.C. Wong, MD, Chairman, Department of Anesthesiology, University of Utah, College of Medicine, 50 North Medical Drive, Salt Lake City, Utah 84132. Equal opportunity/affirmative action employer. Closing date December 31, 1985.

**MISSOURI**

200-bed university pediatric hospital; 200 CV anesthetics/yr. 5500 anesthetics/yr. Full-time university faculty position includes malpractice, life, disability, and health insurance and retirement fringe benefits. Minimum: one year fellowship in pediatric anesthesia. Send CV to John F. Schweiss, MD, Professor and Chairman, Department of Anesthesiology, St. Louis University School of Medicine, 1325 South Grand Boulevard, St. Louis, MO 63104.

**POSITION NOW AVAILABLE**

for board certified/eligible anesthesiologist to join three-member incorporated group with CRNAs in a very progressive community hospital. All types of procedures except open heart. Send CV to Box F23, % *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

**PERMANENT POSITION WANTED**

CRNA—experienced, wishes busy situation, solo or group, best of remuneration. 1-800-521-6750.

## CLASSIFIED ADS

*Anesthesia and Analgesia* makes available classified advertising space for those interested in obtaining positions, or wishing to announce meetings, postgraduate courses, or other events. Display space (minimum ¼ page) is also available through Pharmaceutical Media, Inc. Rates for classified advertising: $.90 per word, minimum twenty words; or $1.00 per word for box number ads. Copy deadline 7 weeks prior to publication. e.g., for the March issue, copy should be received by the 1st of January. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. Ad copy, subject to acceptance by publisher, should be mailed to:

*Anesthesia and Analgesia*
Desk Editorial
Classified Ads
Elsevier Science Publishing Co, Inc,
52 Vanderbilt Avenue, New York, NY 10017.
Make checks payable to Elsevier Science Publishing Co, Inc.

**ANESTHESIOLOGIST**
Board certified anesthesiologist, 3–5 years experience for busy Midwest practice in 700-bed hospital. Send CV to Box H19, % *Anesthesia and Analgesia,* Desk Editorial, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

**ROCKY MTS./SOUTHWEST**
We have career and temporary positions available from solo to large group practice in the Rocky Mts. and Southwest. Expenses paid; partnerships usually available. Please contact Southwest Anesthesia Services, R.R. #9 Box 96 MM, Santa Fe, NM 87501. (505) 983-7371.

**PRIVATE TUTORING AVAILABLE FOR WRITTEN AND ORAL BOARD EXAMS**
Send name, address, and phone to Box ANA 5-84-E, % *Anesthesia and Analgesia,* Desk Editorial, Elsevier Science Publishing Co., Inc., 52 Vanderbilt Avenue, New York, NY 10017.

**FREELANCE ANESTHETISTS**
Temporary & Permanent—Medical Anesthesiologists—CRNAs. Home-based throughout US. If you need an anesthetist call 1-800-521-6750, ALL-STATES MEDICAL PLACEMENT AGENCY, Box 91, LaSalle, MI 48145 or 313-241-1418 (MI).

**CHIEF OF ANESTHESIOLOGY SERVICE**
Applications are being accepted for the position of Chief, Anesthesiology Service at the Veterans Administration Medical Center, Martinez, CA, with a joint appointment in the Department of Anesthesiology, University of California Davis. Applicants should be board certified, have successfully completed accredited residency training in anesthesiology, and have a valid medical license. Experience with research in anesthesiology is desirable. Responsibilities include teaching medical students and residents the principles of anesthesiology. Recruitment will remain open until December 31, 1985. Anticipated appointment date is July 1, 1986. Send curriculum vitae, bibliography, and the names of three references to John R. Eisele Jr, MD, Professor and Chairman, UCD Medical Center, Professional Building, 4301 X Street, Sacramento, CA 95817. An equal opportunity/affirmative action employer.

**ANESTHESIOLOGIST—PHOENIX, ARIZONA AREA**
JCAH Hospital Accreditation—no obstetrics. Board certification highly desirable. Unique group practice offers very early partnership. Available now! Send CV to Box K24, % *Anesthesia and Analgesia,* Desk Editorial, 52 Vanderbilt Avenue, New York, NY 10017.

**UTAH**
The University of Utah seeks an anesthesiologist who is board certified/eligible in anesthesiology and who has completed a formal fellowship in pain. Opportunity to do clinical anesthesia, pain management, and research. Competitive academic salaries at the Instructor level. Send curriculum vitae to K.C. Wong, MD, Chairman, Department of Anesthesiology, University of Utah, College of Medicine, 50 North Medical Drive, Salt Lake City, UT 84132. Equal opportunity/affirmative action employer. Closing date December 31, 1985.

**POSITION WANTED—BE ANESTHESIOLOGIST**
Three years experience. NY and FL licenses. Available for immediate relocation. All offers considered. Reply to Box K25, % *Anesthesia and Analgesia,* Desk Editorial, 52 Vanderbilt Avenue, New York, NY 10017.

**DIRECTOR OF ANESTHESIA DEPARTMENT**
An ideally located, progressive, and family-oriented community offers an excellent professional and living environment for a board-certified anesthesiologist. Serving this Northwest Illinois community is a JCAH-approved 250-bed acute care modern hospital. The operating suite, which serves over 3500 patients per year, is less than one year old. This is a fee-for-service opportunity. The successful candidate will direct a 4-member team of MD anesthesiologists. Please respond to: Stephen A. Menke, Vice President/Chief Operating Officer, Freeport Memorial Hospital, 1045 W. Stephenson St., Freeport, IL 61032.

**ANESTHESIOLOGY RESIDENT**
Currently accepting applications for PGY-3 anesthesiology resident to begin 1/86. Send CV to J. H. Eisele Jr, MD, Chairman, Anesthesiology, UC Davis Medical Center, 2315 Stockton Boulevard, Sacramento, CA 95817. An affirmative action/equal opportunity employer.

**WORLDWIDE ANESTHESIA**
is an exciting organization of anesthesiologists and CRNAs who specialize in relief services and provide qualified candidates for permanent positions throughout the US. To be included in our computerized data base or to recruit from the nation's largest resources of anesthesia personnel, call or write Worldwide Anesthesia, Box 1547, Ukiah, CA 95482. Nationwide 1-800-327-8427. "Over a decade of placement experience."

**ANESTHESIOLOGISTS**
Excellent, prequalified individuals available to join your group on a career or temporary basis. For more information please contact: Southwest Anesthesia Services, PO Box 5719, Santa Fe, New Mexico 87502, (505) 983-7371.

**TUTORING FOR WRITTEN AND ORAL BOARD EXAMS:**
Individual or small group sessions given in New York City, San Francisco, and Hawaii. Unique approach to development of test-taking skills, including mock orals. Basic science emphasis. Include phone number in response. Reply to Box K23, % *Anesthesia and Analgesia,* Desk Editorial, 52 Vanderbilt Avenue, New York, NY 10017.

**ANESTHESIOLOGISTS OVERSEAS**
Short-term service in developing countries. Those wishing to volunteer for participation in educational programs are requested to respond to Anesthesia Overseas, Harry M. Zutz, MD, 4 Rahway Road, Millburn, NJ 07041.

**ANESTHESIOLOGISTS**
Sought by quality-oriented, nationwide referral service for medical–legal consultation. Highly rewarding opportunity. Reply to ExpertNet, 2020 West State Street, Suite 164, Milwaukee, WI 53233. Telephone: (414) 963-8829.

**ANESTHESIOLOGISTS/FACULTY**
Leading medical college expanding their anesthesiology faculty. Primary areas of clinical strength include Trauma, Pediatric, OB-Gyn, and Cardiovascular. State-of-the-art environment with responsibilities conducive to professional development. Resumes of PG-IV to senior faculty. Sunbelt. For further information in strict confidence, contact Celand Enterprises, Executive Search & Ancillary Consulting, 6630 Harwin, Suite 152, Houston, TX 77036. Or phone (713) 974-1357.

# THE LATEST DEVELOPMENTS IN PHARMACOLOGY

## Microspheres and Drug Therapy. Pharmaceutical, Immunological and Medical Aspects

*edited by* **S.S. DAVIS, L. ILLUM, J.G. McVIE** *and* **E. TOMLINSON**

An essential requirement of modern drug therapy is the controlled delivery of the pharmacological agent to its site of action. This volume describes the action of the microspheres in drug targetting techniques, methods and applications of microsphere therapy are evaluated in great detail. The book emphasis is on biological target, pharmaceutical aspects, in vivo action and in vitro usages. The challenge of advanced drug delivery research and developments is used fully in this volume. The design and contents of the book will stimulate further research and help the understanding of this multidisciplinary field.

*1984 xviii + 448 pages*
*Price: US $105.50/Dfl. 285.00*
*ISBN 0-444-80577-X*

## Side Effects of Drugs Annual 9

*edited by* **M.N.G. DUKES**

The Side Effects of Drugs series have gained world-wide acclaim as the most comprehensive, authoritative, up-to-date reference source on adverse reactions. The annuals are published in January of each year and contain the most recent information available screened from some 4000 journals. Annual 9 of this series comprises 51 chapters in which the vast amount of literature on adverse drug reactions is critically reviewed. 'Trends' in adverse reactions are highlighted in the 26 special reviews included which discuss topical issues and therefore provide the reader with a clear guidance to the interpretation of the literature.

*1985: approx. 500 pages*
*Price: US $70.25/Dfl. 190.00*
*ISBN 0-444-90394-1*

## Progress in Medicinal Chemistry, Volume 21

*edited by* **G.P. ELLIS** *and* **G.B. WEST**

This volume presents an excellent balance of reviews on progress made in some of the many long-term challenges to pharmaceutic ingenuity along with treatment of some fields not so commonly encountered. Improvements on sodium cromoglycate's antiallergic action are surveyed, along with the therapy of Parkinson's disease (selegiline) and the antitumour activity of the anthracyclines and of lonidamine, an indolecarboxylic acid. Another such acid, tolnidamine, shows promises as a male contraceptive. Problems encountered in classifying snakes and their venoms constitute a further topic, and the applications of prostacyclin in vascular disorders complete an absorbing volume in a distinguished series.

*1984 viii + 294 pages*
*Price: US $83.25/Dfl. 225.00*
*ISBN 0-444-80603-2*

## Pharmacological and Chemical Synonyms

### 8th Revised Edition

*Compiled by* **E.E.J. MARLER**

This is the latest edition of the world-famous listing of pharmaceutical and chemical synonyms, including pesticides, which was compiled for the first time in 1956.

The book is the most comprehensive source of its kind as more than 4,000 medical and pharmaceutical journals are continually screened for new compounds through the Excerpta Medica Database.

The contents of the book have been converted into a special database to which every new substance name is added, so that the latest information will always be available. The listing now contains approximately 12,000 main terms and all their synonyms.

For people working in the field of pharmacology, pharmaceutics and toxicology, as well as for medical editors and drug regulatory officers, this work will prove to be an indispensable source of information.

*1985 642 pages*
*Price: US $90.75/Dfl. 245.00*
*ISBN 0-444-90359-3*

## Discoveries in Pharmacology

### Volume 2: Haemodynamics, Hormones and Inflammation

*edited by* **M.J. PARNHAM** *and* **J. BRUINVELS**

This book is the second in a series of three volumes dealing with the history of major areas of pharmacology. In this second volume renowned experts describe the way in which discoveries in the cardiovascular, endocrine and inflammatory fields has led to out present state of knowledge.

The areas covered include ergot alkaloids, various anti-hypertensive agents, antithrombotic, anti-anginal and anti-arrythmic drugs.

Steroid hormones and the contraceptive pill, insulin, thyroid hormones and hormones affecting the kidney, immunoinflammatory and anti-inflammatory reactions, histamine receptor antagonists and asthma.

*1984 xviii + 710 pages*
*Price: US $134.50/Dfl. 350.00*
*ISBN 0-444-80578-8*

## Clinically Important Adverse Drug Interactions

### Volume 3: Gastrointestinal, Haematological and Infectious Disease Therapy

*edited by* **J.C. PETRIE**
*Consultant editor* **L.E. CLUFF**

The aim of the three volume series is to provide authoritative guidelines on the clinically important adverse drug interactions associated with the principal drug groups used in clinical practice. This volume in the series is concerned with drug interactions involving gastrointestinal, haematological and infectious disease therapy.

The authors have highlighted the relevant clinical pharmacological information about each drug and deal with the drugs within the group used in clinical practice. This information includes mode of action, pharmacokinetic properties, adverse reactions and drug-host-disease interactions. Pharmacokinetic and pharmacodynamic drug-drug adverse interactions are then discussed against this background of clinical pharmacological information and appropriate emphasis is given to clinically important adverse drug-drug interactions.

*1985 ii + 370 pages*
*Price: US $92.50/Dfl. 250.00*
*ISBN 0-444-80606-7*

**ELSEVIER**

**ELSEVIER SCIENCE PUBLISHERS**

P.O. Box 211, 1000 AE Amsterdam,
The Netherlands.

*in the U.S.A. & Canada:*
**ELSEVIER SCIENCE PUBLISHING CO. INC.,**
P.O. Box 1663, Grand Central Station,
New York, NY 10163, U.S.A.

*The Dutch guilder price is definitive.*
*US $ prices are subject to exchange rate fluctuations. Prices are excl. B.T.W. for Dutch customers.*
*All prices include postage and handling.*

FL 37A193

# INDEX TO ADVERTISERS

American Critical Care
  *Hespan* .......... A12, A13, A14
Anaquest
  *Enlon* .......... A30, A31, A32
  *Forane* .......... A17 thru A20
Breon Laboratories
  *Marcaine* .......... A27, A28
Burroughs Wellcome Co.
  *Tracrium* .......... A23 thru A26, Cover 4
Canadian Anaesthetists' Society Journal
  *Subscriptions* .......... A22
Classified Advertising .......... A41, A42
Kern Medical Center
  *Employment Opportunities* .......... A37
King Saud University
  *Employment Opportunities* .......... A40
Long Island Jewish Medical Center
  *Employment Opportunities* .......... A40
Nellcor, Inc.
  *Pulse Oximeter* .......... A38, A39
Northwestern University Medical School
  *Continuing Education* .......... A37
Novametrix Medical Systems, Inc.
  *Pulse Oximeter* .......... A7
  *Capnogard* .......... A9
  *Transcutaneous Monitor* .......... A11
Ohmeda
  *Biox 3700* .......... A29
Organon Pharmaceuticals
  *Pavulon* .......... Cover 2, A1
Pediatric Anesthesiology Foundation
  *Continuing Education* .......... A37
ProTechPacific
  *ProPillow* .......... Cover 3
  *Strapeze* .......... A8
Hoffman LaRoche, Inc.
  *Injectable Valium* .......... A34, A35, A36
St. Vincent Medical Center
  *Employment Opportunities* .......... A40
Siemens Corporation
  *Servo Ventilator* .......... A15
Traverse Medical Monitors
  *Capnometer* .......... A21
Worldwide Anesthesia Associates
  *Employment Opportunities* .......... A40

*Advertising Office:* Pharmaceutical Media, Inc., 130 Madison Avenue, 6th Floor, New York 10016. Telephone: (212) 685-5010

# Soothing news for busy anesthesiologists

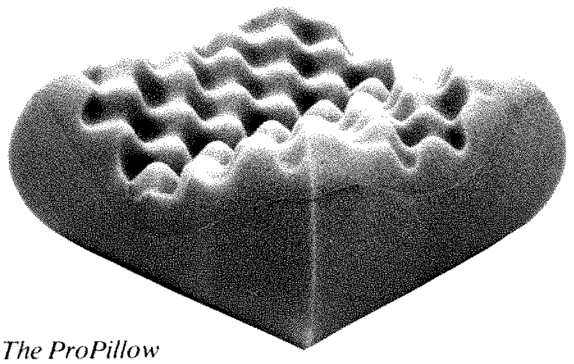
Dr. Smith was having another busy day in surgery. One Swan-Ganz placement had been unusually time-consuming. Plus the patient had been difficult to intubate. To top it off, the pump time had been excessive.

Down the hall, Dr. Jones had a marathon case involving a young woman undergoing a tuboplasty for infertility. Finally, 5½ hours later the surgeons were closing the skin. He heaved a sigh of relief and automatically leveled the table from the previous several hours where the Trendelenberg position had been necessary.

But these two stories don't end here. About 28 days later, *both patients had a bald spot about the size of a silver dollar at the occiput. . . exactly where their heads were resting on the table for hours on end.* They were each advised by their surgeons that they had a 50% chance of their hair growing back within the next year. But there was an equal chance that their hair wouldn't grow back at all. The anesthesiologists on both cases were never told of the problem.

## The ProPillow takes the pressure off

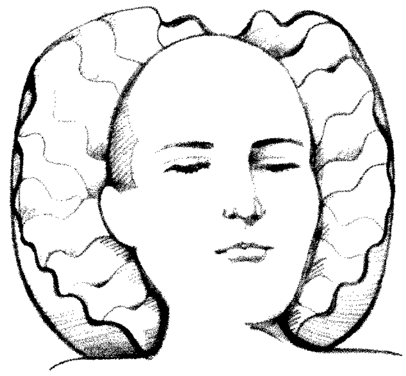
The ProPillow Anesthesia Pillow helps "take off the pressure" to the circulation of the face and scalp during prolonged anesthesia. It's unique "hills and valleys" construction creates a protective effect by evenly distributing the weight of the head and neck. Result: no more pressure in one area greater than any other area. And those precipitous swings in blood pressure are less likely to result in ischemia to the scalp. All this lessens the chance of post-op alopecia.



*The ProPillow Anesthesia Pillow*

## The end of the juggling act

The ProPillow lets you off gracefully from attempts to juggle the heavy head (10 lbs.) during intubation. The ProPillow Anesthesia Pillow stabilizes (by gently gripping) the patient's head in the neutral, "sniffing", position. It even helps free up one of your hands when you're using a mask for short cases.



*The ProPillow Anesthesia Pillow stabilizes the head, supports the neck and helps take the pressure off.*

## An eye for details

Awake patients really appreciate the comfort of the ProPillow Anesthesia Pillow. Especially the eye patients who are undergoing removal of cataracts with intra-ocular lens implants. And the ProPillow fits inside the frame used by Opthalmologists during this tedious microsurgery. Less squirming. . . and possibly sedation required.

## And the price is right

Because of the ProPillow's reasonable price, some say we should call it disposable. But it is made to last for up to 50 cases. You can use a nurse's bouffant cap to cover the ProPillow. Or even spot wash and air-dry it. It's made from a bright blue, breathable, resilient polyurethane foam that's 100% non-allergenic and non-irritating to skin.

It's easy to order the ProPillow Anesthesia Pillow! Call us **TOLL FREE** at **(800) 227-0517 outside California**, or **(800) 554-5541 inside California.** Or, give this page to your head nurse or purchasing agent to get the ProPillow promptly. We ship within 24 hours. *Pediatric Size available, ask for details.

**ProTechPacific**
**1221 Andersen Drive**
**San Rafael, CA 94901**

Makers of the **ProPillow Anesthesia Pillow, NECK-PIL-O Neck Support Pillow, DIXSEY Hip Abduction pillow** and the new **STRAPEZE *Velcro Endotracheal Tube stabilizer.**

# ANNOUNCING:
# The new, easily identifiable, economical, shatter-resistant, 10 ml, multiple-dose vial

**(100 mg atracurium besylate per vial).**

**Multiple-dose vials can reduce the amount of Tracrium subject to waste by as much as 22% when compared to ampules!***

*Data on file, Burroughs Wellcome Co.

**TRACRIUM**® INJECTION
(atracurium besylate)

Wellcome
**Burroughs Wellcome Co.**
Research Triangle Park
North Carolina 27709

Copr. © 1985 Burroughs Wellcome Co. All rights reserved. 85TRA10

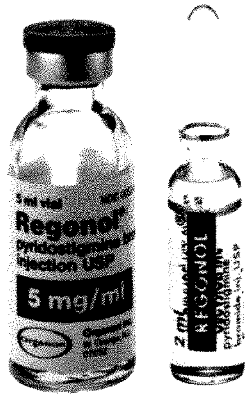
ISSN 000-2999
Volume 64, Number 12, December 1985

Acc.
9.12.86

# Anesthesia and Analgesia

Journal of the International Anesthesia Research Society
Oldest Publication in the Specialty—Established 1922

In
**Reversal**
of nondepolarizing
muscle relaxants,
don't look for what's better...
...look for what's best



**Regonol®**
(pyridostigmine
bromide injection, USP)
when compared to neostigmine

☐ Clinically fewer side effects
☐ Significantly lower degree and incidence of:
  1) Bradycardia
  2) Salivation
  3) Gastrointestinal stimulation
☐ Wide margin of safety[1,2]

Organon
**Organon Pharmaceuticals**
A Division of Organon Inc.
West Orange, N.J. 07052

OR-5091

**Regonol** (pyridostigmine bromide injection USP)

**BRIEF SUMMARY**—(Please consult full package insert, enclosed in every package, before using Regonol)

**INDICATIONS**—Pyridostigmine bromide is useful as a reversal agent or antagonist to nondepolarizing muscle relaxants

**CONTRAINDICATIONS**—Known hypersensitivity to anticholinesterase agents: intestinal and urinary obstructions of mechanical type.

**WARNINGS**—Pyridostigmine bromide should be used with particular caution in patients with bronchial asthma or cardiac dysrhythmias. Transient bradycardia may occur and be relieved by atropine sulfate. Atropine should also be used with caution in patients with cardiac dysrhythmias. When large doses of pyridostigmine bromide are administered, as during reversal of muscle relaxants, prior or simultaneous injection of atropine sulfate is advisable. Because of the possibility of hypersensitivity in an occasional patient, atropine and anti-shock medication should always be readily available

When used as an antagonist to nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance and there should be continuous patient observation. Satisfactory recovery may be defined by a combination of clinical judgement, respiratory measurements and observation of the effects of peripheral nerve stimulation. If there is any doubt concerning the adequacy of recovery from the effects of the nondepolarizing muscle relaxant, artificial ventilation should be continued until all doubt has been removed.

***Use in Pregnancy***—The safety of pyridostigmine bromide during pregnancy or lactation in humans has not been established. Therefore its use in women who are pregnant requires weighing the drug's potential benefits against its possible hazards to mother and child.

**ADVERSE REACTIONS**—The side effects of pyridostigmine bromide are most commonly related to overdosage and generally are of two varieties, muscarinic and nicotinic. Among those in the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and diaphoresis. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and weakness. Muscarinic side effects can usually be counteracted by atropine. As with any compound containing the bromide radical, a skin rash may be seen in an occasional patient. Such reactions usually subside promptly upon discontinuance of the medication. Thrombophlebitis has been reported subsequent to intravenous administration.

**DOSAGE AND ADMINISTRATION**—When pyridostigmine bromide is given intravenously to reverse the action of muscle relaxant drugs, it is recommended that atropine sulfate (0.6 to 1.2 mg) or glycopyrrolate in equipotent doses be given intravenously immediately prior to or simultaneous with its administration. Side effects, notably excessive secretions and bradycardia, are thereby minimized. Reversal dosages range from 0.1-0.25 mg./kg. Usually 10 or 20 mg. of pyridostigmine bromide will be sufficient for antagonism of the effects of the nondepolarizing muscle relaxants. Although full recovery may occur within 15 minutes in most patients, others may require a half hour or more. Satisfactory reversal can be evident by adequate voluntary respiration, respiratory measurements and use of a peripheral nerve stimulator device. It is recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. Once satisfactory reversal has been attained, recurarization has not been reported.

Failure of pyridostigmine bromide to provide prompt (within 30 minutes) reversal may occur, e.g., in the presence of extreme debilitation, carcinomatosis, or with concomitant use of certain broad spectrum antibiotics or anesthetic agents, notably ether. Under these circumstances ventilation must be supported by artificial means until the patient has resumed control of his respiration.

**HOW SUPPLIED**—Regonol is available in:

5 mg./ml.: 2 ml. ampuls—boxes of 25—NDC-0052-0460-02
5 ml. vials—boxes of 25—NDC-0052-0460-05

**REFERENCES:**

1. Gyermek L: Clinical studies on the reversal of the neuromuscular blockade produced by pancuronium bromide. 1 The effects of glycopyrrolate and pyridostigmine. *Curr Ther Res* 18:377-386, 1975.
2. Ravin MB: Pyridostigmine as an antagonist of d-tubocuranrine-induced and pancuronium-induced neuromuscular blockade. *Anesth Analg—Curr Res* 54:317-321, 1975

Organon

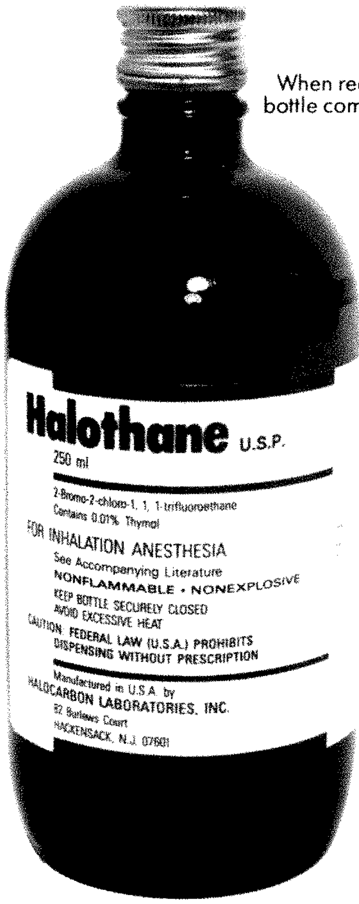
**Organon Pharmaceuticals**
A Division of Organon Inc.
West Orange, N.J. 07052

OR-5091

---

# HALOTHANE U.S.P.

## Produced by Halocarbon Laboratories, Inc.


Halothane U.S.P.
250 ml
2-Bromo-2-chloro-1, 1, 1-trifluoroethane
Contains 0.01% Thymol
FOR INHALATION ANESTHESIA
See Accompanying Literature
NONFLAMMABLE • NONEXPLOSIVE
KEEP BOTTLE SECURELY CLOSED
AVOID EXCESSIVE HEAT
CAUTION: FEDERAL LAW (U.S.A.) PROHIBITS DISPENSING WITHOUT PRESCRIPTION
Manufactured in U.S.A. by
HALOCARBON LABORATORIES, INC.
82 Burlews Court
HACKENSACK, N.J. 07601

When requested
bottle comes with collar.

- First Maker of Fluorinated Anesthetics in the U.S.A.
- Pioneer in Anesthetic Purity
- Lowest Price of Any Potent Anesthetic

**HALOCARBON**
LABORATORIES, INC.
P.O. Box 833
Hackensack, NJ 07602
(201) 343-8703

# ANNOUNCING:
# The new, easily identifiable, economical, shatter-resistant, 10 ml, multiple-dose vial

(100 mg atracurium besylate per vial).

Multiple-dose vials can reduce the amount of Tracrium subject to waste by as much as 22% when compared to ampules!*

*Data on file, Burroughs Wellcome Co.

**TRACRIUM® INJECTION**
(atracurium besylate)

Wellcome

**Burroughs Wellcome Co.**
Research Triangle Park
North Carolina 27709

Copr. © 1985 Burroughs Wellcome Co. All rights reserved. 85TRA10

# Anesthesia and Analgesia

## Journal of the International Anesthesia Research Society

3645 Warrensville Center Road, Cleveland, Ohio 44122 Telephones: (216) 295-1124 or 295-1130

## Editorial Board

### Editor in Chief

Nicholas M. Greene, MD, New Haven, Connecticut

### Editors

David R. Bevan, MA, MB, BChir, Montreal, Quebec, Canada
D. Ryan Cook, MD, Pittsburgh, Pennsylvania
Michael J. Cousins, MD, FFARACS, FFARCS, Adelaide, South Australia
Benjamin G. Covino, PhD, MD, Boston, Massachusetts
Norig Ellison, MD, Philadelphia, Pennsylvania
Mieczyslaw Finster, MD, New York, New York
Alison B. Froese, MD, Kingston, Ontario, Canada
Edward D. Miller Jr, MD, Charlottesville, Virginia
Daniel M. Philbin, MD, Boston, Massachusetts
Cedric Prys-Roberts, MA, DM, PhD, Bristol, United Kingdom
J. Gerald Reves, MD, Durham, North Carolina
John H. Tinker, MD, Iowa City, Iowa
K.C. Wong, MD, PhD, Salt Lake City, Utah

### Book Review Editor

Norig Ellison, MD, Philadelphia, Pennsylvania

Editorial correspondence and manuscripts should be addressed to: NICHOLAS M. GREENE, MD, Editor in Chief, *Anesthesia and Analgesia*, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510 (Telephone: 203-785-4703). For information concerning preparation of manuscripts see "A Guide for Authors" published quarterly in the Journal. All articles published in this Journal become the property of the International Anesthesia Research Society. Reproduction in whole or part is not permitted except by written consent of the publisher and the author.

Books for review should be sent directly to the Book Review Editor, NORIG ELLISON, MD, Department of Anesthesia, University of Pennsylvania, Philadelphia, Pennsylvania 19104.

Reprints: For single copies, write directly to the senior author at the address listed on the title page. Quantity orders (minimum 100) processed through ELSEVIER SCIENCE PUBLISHING CO, INC, 52 Vanderbilt Avenue, New York, NY 10017, prices on request.

The International Anesthesia Research Society is a nonprofit, scientific, and educational corporation in the state of Ohio. Members of the Board of Trustees of the Society are: Douglas B. Craig, MD, Bruce F. Cullen, MD, E. Paul Didier, MD, Judith H. Donegan, MD, PhD, Noel W. Lawson, MD, John T. Martin, MD, Emerson A. Moffitt, MD, Dean H. Morrow, MD, Robert K. Stoelting, MD, and John L. Waller, MD. Emeritus Trustees are: Paul R. Dumke, MD, Kenneth K. Keown, MD, Morris T. Nicholson, MD, B.B. Sankey, MD, and T. H. Seldon, MD.

*Anesthesia and Analgesia* (ISSN 0003-2999) is issued monthly for the IARS in one indexed volume per year by Elsevier Science Publishing Co, Inc, 52 Vanderbilt Avenue, New York, NY 10017. Printed in USA. © 1985 International Anesthesia Research Society. Second class postage paid at New York, NY and at additional offices.

Subscription information for 1986 applying to IARS members: USA and possessions, $50.00 per year, in all other countries $61.00. Membership is available to individuals with doctorate degrees in medicine, osteopathy, dentistry, veterinary medicine, or other disciplines who are engaged in active clinical practice of or research in anesthesiology. ASSOCIATE MEMBERSHIP is available to individuals certified, licensed, or accredited in anesthesia-related professions (CRNA, CRTT, RRT, Physician Assistant). EDUCATIONAL MEMBERSHIP (half the full member price) is available to interns, residents, students in nurse anesthesia and related training programs, for a 2- or 3-year period only upon completion of application including certification by applicant's program director.

All membership payments and correspondence regarding IARS member subscriptions should be sent to: Emerson A. Moffitt, MD, Executive Secretary, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, Ohio 44122.

Subscription information for 1986 applying to non-IARS members: Institutions, $95.00; nonmember individuals, $50.00. Outside of the USA and possessions, please add $11.00 for surface postage and handling. For airmail, add $40.00 in USA, Canada, and Mexico, $23.00 for surface airlift to Europe, $36.00 for surface airlift to Japan, and $93.00 for airmail to the rest of the world. Postmaster: Send address changes to: *Anesthesia and Analgesia*, Elsevier Science Publishing Co, Inc, 52 Vanderbilt Avenue, New York, NY 10017.

Orders and inquiries regarding institutional and nonmember individual subscriptions should be directed to: Journals Fulfillment, Elsevier Science Publishing Co, Inc, 52 Vanderbilt Avenue, New York NY 10017. Subscriptions are entered for the calendar year, January–December.

Correspondence inquiries regarding IARS member subscriptions should be sent to the IARS at the Cleveland, Ohio address above. Correspondence regarding all other subscriptions should be sent to Elsevier.

Advertising inquiries should be addressed to: Pharmaceutical Media, Inc, 130 Madison Avenue, New York, NY 10016. The appearance of advertising in publications of the International Anesthesia Research Society does not constitute a guarantee or endorsement of the quality or value of such product or of the claims made for it by its manufactuer. Discussions, views, and recommendations as to medical procedures, choice of drugs, and drug dosages are the responsibility of the authors. Every effort has been made to ensure the accuracy of the information. The editor, publisher, or the Society, however, must disclaim any responsibility or liability. Readers are advised to check package insert information for each drug before administration.

See classified ads section for submission of classified material.

Single issues: Single copy information available from Elsevier Science Publishing Co, Inc, upon request. Back volume (all issues prior to 1983) information available from IARS.

Anesthesia
and Analgesia

# Contents

**Volume 64, Number 12, December 1985**

## SCIENTIFIC ARTICLES

Blunting of Stress Responses in the Pulmonary Circulation of Infants by Fentanyl *Paul R. Hickey, Dolly D. Hansen, David L. Wessel, Peter Lang, Richard A. Jonas, and E. Marsha Elixson* 1137

Anesthesia, Amnesia, and the Memory/Awareness Distinction *Eric Eich, John L. Reeves, and Ronald L. Katz* 1143

Halothane Effects on Subendocardial Oxygen Supply–Demand Balance: Estimation from Intramyocardial Tissue Pressure and Left Ventricular Pressure *Young D. Kim, David Nematzadeh, David E. Lees, Pamela H. Wolf, John C. Rose, Peter A. Kot, and Thomas E. Macnamara* 1149

Thiopental Requirements May Be Increased in Children Reanesthetized at Least One Year after Recovery from Extensive Thermal Injury *Charles J. Coté and A. John Petkau* 1156

Epidural Ketamine for Control of Postoperative Pain *Jose-Adolfo Islas, Jorge Astorga, and Miguel Laredo* 1161

Central Serotonin Depletion: Effect on Blood Pressure during Anesthesia *John S. Althaus, Judy J. Beckman, and Edward D. Miller Jr* 1163

Transient Inhibitory Effect of Isoflurane upon Oxidative Halothane Metabolism *Vera Fiserova-Bergerova and Damian F. Dolan* 1171

Disuse and *d*-Tubocurarine Sensitivity in Isolated Muscles *Barbara E. Waud, Yoshikiyo Amaki, and Douglas R. Waud* 1178

Effects of Volatile Anesthetics or Fentanyl on Hepatic Function in Cirrhotic Rats *Jeffrey M. Baden, Yashdev R. Kundomal, Michael E. Luttropp Jr, Mervyn Maze, and Jon C. Kosek* 1183

Intravenous Lidocaine as a Suppressant of Coughing during Tracheal Intubation *Hidekazu Yukioka, Noritada Yoshimoto, Kiyoji Nishimura, and Mitsugu Fujimori* 1189

Does Intravenous Lidocaine Prevent Laryngospasm after Extubation in Children? *Pernille Leicht, Torben Wisborg, and Bent Chraemmer-Jørgensen* 1193

Decreased Incidence and Mortality of Anaphylaxis to Chymopapain *Jonathan Moss, Michael F. Roizen, Eugene J. Nordby, Ronald Thisted, Jeffrey L. Apfelbaum, Bruce D. Schreider, and Daniel J. McDermott* 1197

Verapamil Does Not Alter Succinylcholine-Induced Increases in Serum Potassium during Halothane Anesthesia in Normal Dogs *Jeffrey L. Roth, Michael Nugent, and Gerald A. Gronert* 1202

## CLINICAL REPORTS

Potential Hazards of Transcatheter Serial Epidural Phenol Neurolysis *Dennis W. Coombs* 1205

Bedside Diagnosis of Bilateral Diaphragmatic Paralysis in a Ventilator-Dependent Patient after Open-Heart Surgery *Karen A. Brown, V. Hoffstein, and Robert J. Byrick* 1208

The Effect of Intravenous Lidocaine on the Increase in Intraocular Pressure Induced by Tracheal Intubation *Benjamin Drenger, Jacob Pe'er, David BenEzra, Ruth Katzenelson, and Joseph T. Davidson* 1211

Arrhythmias during Venous Cannulation prior to Pulmonary Artery Catheter Insertion *Roger L. Royster, William E. Johnston, Glenn P. Gravlee, Stanley Brauer, and Dan Richards* 1214

Peripheral Nerve Stimulation Through a Local Anesthetic Path: A Modified Koons Technique *Thomas G. Johans and George Carr* 1217

Prolonged Neuromuscular Blockade with Vecuronium in a Patient Treated with Magnesium Sulfate *Raymond S. Sinatra, Beverly K. Philip, J. Stephen Naulty, and Gerard W. Ostheimer* 1220

## LETTERS TO THE EDITOR

Midazolam Maleate and Hydrochloride *J. W. Dundee and P. Kawar* 1223

The Effect of Chloroprocaine on Neonatal Neurobehavior *Betty R. Kuhnert and Patricia L. Linn* 1223

Humidifiers Are Unjustified in Adult Anesthesia *R. K. Baumgarten* 1224

Seizures from Isoflurane? *Arthur S. Keats* 1225

In Response *Jayson A. Hymes* 1226

Seizures with Etomidate Anesthesia *Walter Krieger, Jack Copperman, and Kenneth D. Laxer* 1226

Possible Potentiation by Hydroxyzine of Metoclopramide's Undesirable Side Effects *Jean L. Fouilladieu, Mireille Hosanski, Kathleen McGee, Milan Korvin, Pierre Bonnette, Yves Joulin, and Christian Conseiller* 1227

## BOOK REVIEWS

A Calculus of Suffering. Pain, Professionalism, and Anesthesia in Nineteenth Century America. Martin S. Pernick. *Leroy D. Vandam* 1229

Nitrous Oxide/$N_2O$. Edmond I. Eger II, ed. *Jeffrey B. Gross* 1230

Guest Reviewers for 1985 1231

Annual Index 1233

Author Index 1235

Subject Index 1249

# INTERNATIONAL ANESTHESIA RESEARCH SOCIETY
# 60th CONGRESS—March 15–19, 1986—
# Caesars Palace Hotel, Las Vegas, Nevada

## PRELIMINARY MEETING INFORMATION

**Program/Registration Mailing:** The preliminary program, with daily schedule of presentations, will be sent out in mid-December to all IARS members. This will include registration card, hotel card, social activities and spouse program. (IARS members outside of North America who plan to attend the meeting can receive this material by airmail upon request.) Non-IARS members who wish to receive meeting/membership information should contact the Cleveland office.

| | |
|---|---|
| Schedule: | Registration: Saturday, March 15—1–5 PM (continues daily)<br>Scientific Program: Sunday, March 16, through Wednesday, March 19<br>Exhibits: Sunday, March 16, through Tuesday, March 18 |
| Program: | • T.H. Seldon Distinguished Lecture—Dr. J. Alfred Lee, Essex, England<br>• 26 Review Course Lectures<br>• Panels: Outpatient Anesthesia, Cardiovascular Anesthesia<br>• Over 100 Scientific Papers<br>• Scientific Poster Presentations<br>• Theme Luncheon Sessions<br>• Scientific Exhibits |
| Technical (Commercial) Exhibits: | Including a number of company sponsored Product Seminars |
| Spouse Program: | "Effective Tax Strategies" Seminar; area tours and other activities and presentations of interest. |
| Reduced Air Fare: | A special discounted fare will be available through United Airlines for IARS registrants. |
| CME Credit: | AMA/ACCME Category 1 (31 hr, est.) AANA credit to be confirmed. |

SCIENTIFIC EXHIBITS: Applications for scientific exhibit space are available from the IARS office. There is no absolute deadline for submission of applications. However, availability of space in the exhibit area will be a factor in considering applications received after January 1, 1986.

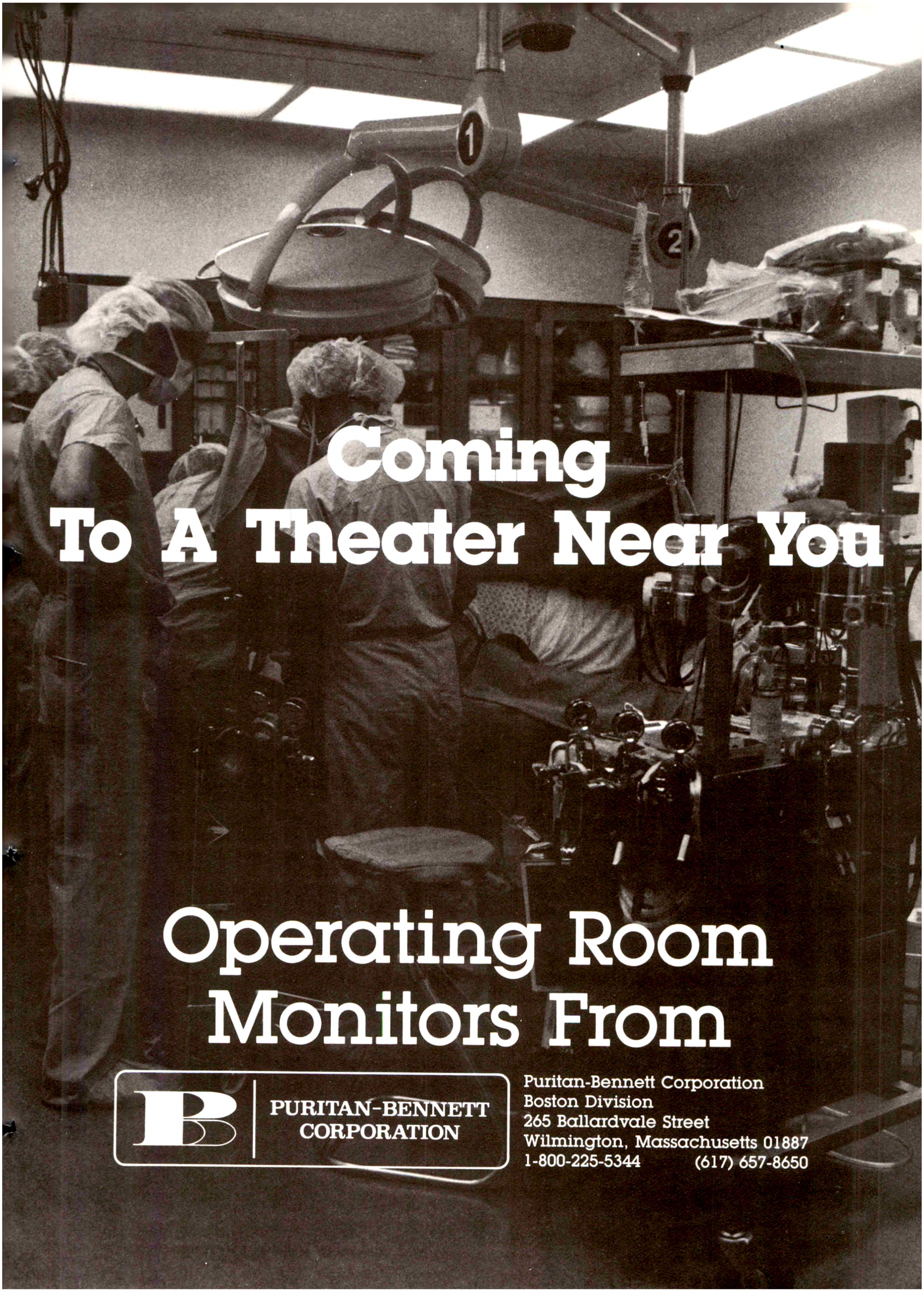
ARTS AND CRAFTS EXHIBIT: Responding to interest expressed by a number of members, the IARS will for the first time include an arts and crafts exhibit at the 1986 meeting. If you or your spouse would like to enter your personally done art or craft work, the rules and entry blanks are available from the Cleveland office. **The deadline for entry is January 31, 1986.**

---

International Anesthesia Research Society
3645 Warrensville Center Road, Cleveland, OH 44122
Tel: (216) 295-1124

( ________ ) Please send rules and entry blank for Arts and Crafts Exhibit.
( ________ ) Please send application for Scientific Exhibit space.

(Name) ____________________________________________
(Mail Address) ____________________________________________
____________________________________________



Puritan-Bennett Corporation
Boston Division
265 Ballardvale Street
Wilmington, Massachusetts 01887
1-800-225-5344 (617) 657-8650

# Resuscitation

**Managing Editor**
**John B. McCabe,** Wright State University
School of Medicine,
Dept. of Emergency Medicine,
P.O. Box 927, Dayton, Ohio 45401, U.S.A.

**Founding Editor**
**H. Hillman,** Unity Laboratory,
Dept. of Human Biology and Health, University of Surrey,
Guildford, Surrey, U.K.

## Aims and Scope

**RESUSCITATION** is a quarterly international interdisciplinary medical journal. The papers published deal with the etiology, pathophysiology, diagnosis and treatment of acute diseases. Clinical and experimental research, reviews and case histories will be published.

## Editorial Policy

The originality of content of papers submitted and the quality of the work on which they are based is the prime consideration of the editors. Authors whose papers have been rejected for publication in the journal may respond to detailed comments again, and resubmit their paper, but the decision of the Editor-in-Chief advised by reviewers is final.

## Editorial Board

**F.W. Ahnefeld** *(Ulm)*
**M.S. Albin** *(San Antonio, TX)*
**D.K. Anderson** *(Cincinnati, OH)*
**C. Brown** *(Columbus, OH)*
**S. Bursztein** *(Haifa)*
**H.H. Chen** *(Beijing)*
**A. Gilston** *(London)*
**M. Goulon** *(Paris)*
**G.C. Hamilton** *(Dayton, OH)*
**M.S. Jastremski** *(Syracuse, NY)*
**K. Little** *(Edinburgh)*
**A. Lowenthal** *(Antwerp)*
**N. Nishimura** *(Tokyo)*
**M.M. Pollack** *(Washington DC)*
**S.H. Ralston** *(West Lafayette, IN)*
**J. Verdura** *(Mexico)*
**D. Zideman** *(London)*

## Consulting Editors

**V.A. Negovsky** *(Moscow)*
**P. Safar** *(Pittsburgh, PA)*

## Resuscitation

*An exciting journal for the dissemination of clinical and basic science research relating to this field.*

## Subscription Information

**1986:** Volume 14 (1 vol. in 4 issues)
Subscription rate: US $114.00
Personal rate: US $45.00
(prices include postage and handling)
ISSN 0300-9572

**ELSEVIER**

Send your orders to:
**Elsevier Scientific Publishers Ireland, Ltd.,** P.O. Box 85, Limerick, Ireland

Requests for free sample copies should be sent to:

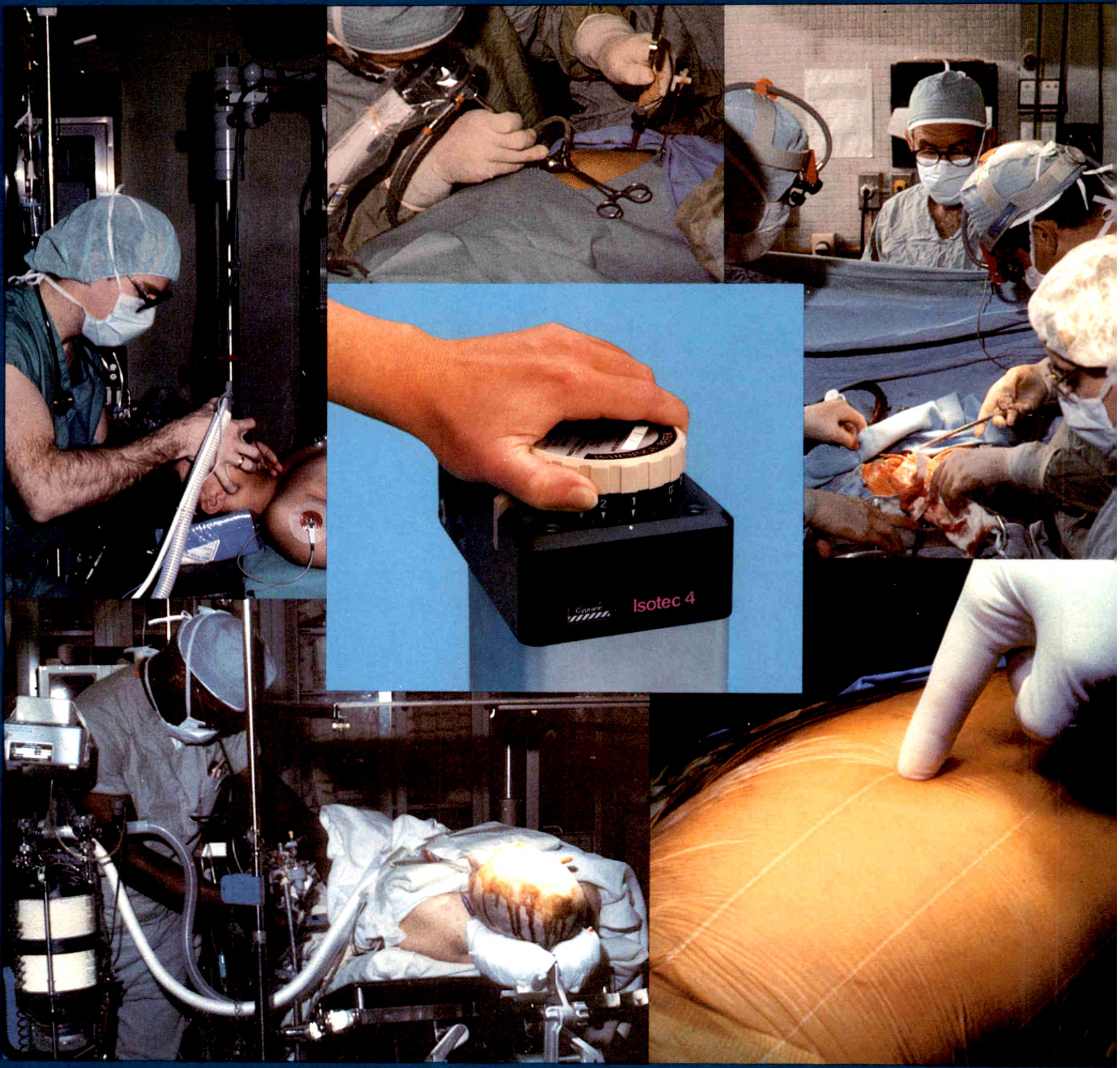
In the U.S.A. and Canada
Journal Information Center
ELSEVIER SCIENCE PUBLISHERS,
52 Vanderbilt Avenue, New York, NY 10017, U.S.A.

In all other countries:
ELSEVIER SCIENTIFIC PUBLISHERS
IRELAND LTD.,
P.O. Box 85, Limerick, Ireland

The US $ price is definitive.

FL37A336

# Forane® (isoflurane)
# The Versatile Anesthetic



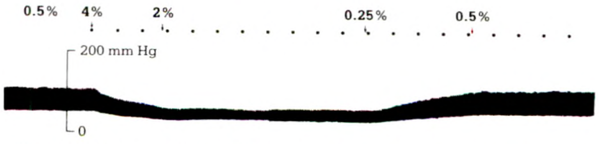
**Anaquest**

Forane® (isoflurane)

# Forane® (isoflurane)
# The Versatile Anesthetic

## A hypotensive agent for craniotomy and clipping of aneurysms

Isoflurane may be used as both anesthetic and hypotensive agent, providing for precise control of blood pressure throughout procedures such as clipping of cerebral aneurysms.[1]



Blood pressure tracing demonstrating the rapid response of systemic blood pressure to changes in inspired isoflurane concentration. The arrows indicate the changes in isoflurane concentration and the dots mark 1-min intervals. Mean blood pressure during the normotensive period was 70 mm Hg and 40 mm Hg during the hypotensive phase.[1]

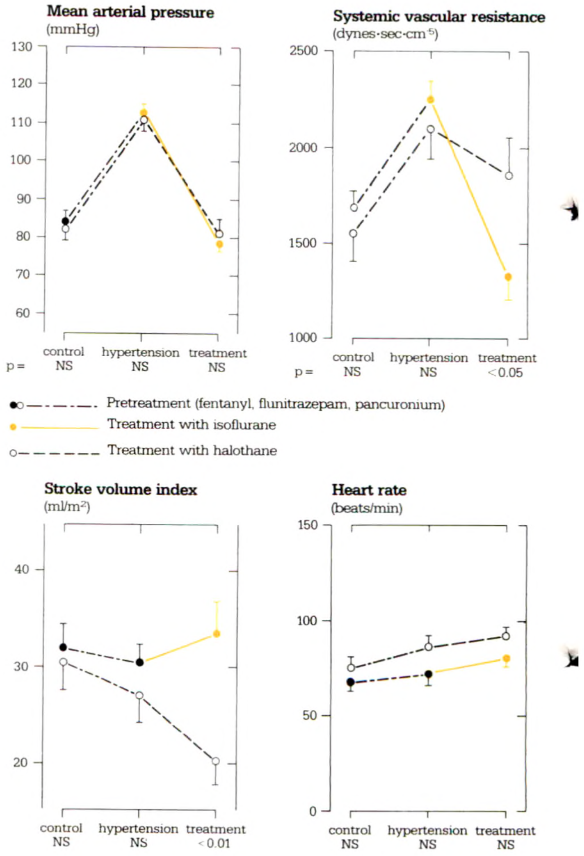
## Control of intracranial pressure for craniotomy and excision of space-occupying lesion

Isoflurane causes no increase in intracranial pressure (ICP) when $PaCO_2$ is controlled at 25-30 torr, and ICP may be readily lowered *during surgery* by decreasing $PaCO_2$.[2]

## Control of hypertension during coronary artery bypass surgery

Control of intraoperative hypertension may be achieved with isoflurane by lowering peripheral vascular resistance (left ventricular afterload) generally without depressing stroke volume or increasing heart rate. These effects can be of particular benefit in patients with compromised left ventricular function. Halothane is equally effective in lowering blood pressure without increasing heart rate, but it decreases stroke volume.

Treatment of hypertension with either isoflurane or halothane anesthesia in patients undergoing coronary artery bypass surgery (Adapted from Hess et al[3]).



## Potentiation of relaxants for orthopedic surgery

With isoflurane anesthesia, profound surgical muscle relaxation can be provided with one-third to two-thirds the usual relaxant dose (pancuronium, d-tubocurarine or atracurium).[4,5] Thus the recovery period may be shortened and the need for reversal agents reduced by the rapid elimination of isoflurane.

---

## Stability of heart rhythm when full hemostatic doses of epinephrine are needed

"Isoflurane, like enflurane, produces stable cardiac rhythm and, unlike halothane, does not sensitize the myocardium to the effects of catecholamines."[6]

---

## A rapid recovery with few post-anesthetic symptoms for outpatient surgery

"Isoflurane is eliminated more rapidly than any other potent modern inhaled anesthetic."[7] (Blood-gas partition coefficient, only 1.4)

Anesthesia using isoflurane in a mixture of oxygen and air produced a significantly lower incidence of nausea and vomiting following outpatient laparoscopy than anesthesia that included nitrous oxide.[8]

**Post-laparoscopy Nausea (N) and Vomiting (V)**

| Group | No. of Patients | No. of Patients with N or N&V |
|---|---|---|
| fentanyl, $N_2O$, $O_2$ | 37 | 23 (62%)* |
| isoflurane, fentanyl, $O_2$ | 20 | 6 (30%) |
| isoflurane, $O_2$ | 20 | 5 (25%) |

Adapted from Alexander et al[8] *$p<0.05$

**References:**

1. Lam AM, Gelb AW: Cardiovascular effects of isoflurane-induced hypotension for cerebral aneurysm surgery. Anesth Analg 62:742-748, 1983.
2. Adams RW et al: Isoflurane and cerebrospinal fluid pressure in neurosurgical patients. Anesthesiology 54:97-99, 1981. 3. Hess W et al: Comparison of isoflurane and halothane when used to control intraoperative hypertension in patients undergoing coronary artery bypass surgery. Anesth Analg 62:15-20, 1983. 4. Miller RD et al: Comparative neuromuscular effects of pancuronium, gallamine, and succinylcholine during Forane and halothane anesthesia in man. Anesthesiology 35:509-514, 1971. 5. Tracrium® (atracurium besylate) prescribing information, Burroughs Wellcome Co., Research Triangle Park, NC 27709. 6. Wade JG, Stevens WC: Isoflurane: an anesthetic for the eighties? Anesth Analg 60(9):666-682, 1981.
7. Eger EI II: Isoflurane, a compendium and reference, Ohio Medical Anesthetics, Madison, WI, 1981. 8. Alexander GD et al: The role of nitrous oxide in postoperative nausea and vomiting. Anesth Analg 63:175, 1984.

For complete use information, please see following page.

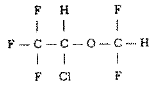
**Forane® . . . a product of original Anaquest research**
**(isoflurane)**

# Forane®... The Versatile Anesthetic
## (isoflurane)

CAUTION: Federal Law Prohibits Dispensing without Prescription

**DESCRIPTION**

FORANE (isoflurane) is a nonflammable general inhalation anesthetic agent. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:



$$\mathrm{F_3C{-}CHCl{-}O{-}CHF_2}$$

Some physical constants are:

| | | |
|---|---|---|
| Molecular weight | | 184.5 |
| Boiling point at 760 mm Hg | | 48.5 °C (uncorr.) |
| Refractive index $n_D^{20}$ | | 1.2990-1.3005 |
| Specific gravity 25 °/25 °C | | 1.496 |
| Vapor pressure in mm Hg** | 20 °C | 238 |
| | 25 °C | 295 |
| | 30 °C | 367 |
| | 35 °C | 450 |

**Equation for vapor pressure calculation:

$\log_{10}P_{vap} = A + \frac{B}{T}$ where: A = 8.056
B = −1664.58
T = °C + 273.16 (Kelvin)

| | |
|---|---|
| Partition coefficients at 37 °C | |
| Water/gas | 0.61 |
| Blood/gas | 1.43 |
| Oil/gas | 90.8 |
| Partition coefficients at 25 °C - rubber and plastic | |
| Conductive rubber/gas | 62.0 |
| Butyl rubber/gas | 75.0 |
| Polyvinyl chloride/gas | 110.0 |
| Polyethylene/gas | ~2.0 |
| Polyurethane/gas | ~1.4 |
| Polyolefin/gas | ~1.1 |
| Butyl acetate/gas | ~2.5 |
| Purity by gas chromatography | >99.9% |
| Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec. and 23 °C | None |
| Lower limit of flammability in oxygen or nitrous oxide at 900 joules/sec. and 23 °C | Greater than useful concentration in anesthesia |

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, ethereal odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave U.V. light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

**CLINICAL PHARMACOLOGY**

FORANE (isoflurane) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is as follows:

| Age | 100% Oxygen | 70% $N_2O$ |
|---|---|---|
| 26 ± 4 | 1.28 | 0.56 |
| 44 ± 7 | 1.15 | 0.50 |
| 64 ± 5 | 1.05 | 0.37 |

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal $PaCO_2$, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administered epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 mL of 1:200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE, THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

**Pharmacokinetics:** Isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

**INDICATIONS AND USAGE**

FORANE (isoflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

**CONTRAINDICATIONS**

Known sensitivity to FORANE (isoflurane) or to other halogenated agents.

Known or suspected genetic susceptibility to malignant hyperthermia

**WARNINGS**

Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions.

FORANE (isoflurane) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

**PRECAUTIONS**

**General:** As with any potent general anesthetic, FORANE (isoflurane) should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

**Information to Patients:** Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

**Laboratory Tests:** Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

**Drug Interactions:** Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of $N_2O$.

See CLINICAL PHARMACOLOGY.

**Carcinogenesis:** Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at 1/2, 1/8 and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice which were given the same background gases, but not the anesthetic.

**Pregnancy Category C:** Isoflurane has been shown to have a possible anesthetic-related fetotoxic effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

**Malignant Hyperthermia:** In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the $CO_2$ absorption system (hot canister). $PaO_2$ and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

**ADVERSE REACTIONS**

Adverse reactions encountered in the administration of FORANE (isoflurane) are in general dose dependent extensions of pharmacophysiologic effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting and ileus have been observed in the postoperative period.

As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia.

**OVERDOSAGE**

In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

**DOSAGE AND ADMINISTRATION**

**Premedication:** Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

**Inspired Concentration:** The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for isoflurane;
b) vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula:

$$\%\ \text{isoflurane} = \frac{100\ P_V\ F_V}{F_T\ (P_A - P_V)}$$

where: $P_A$ = Pressure of atmosphere
$P_V$ = Vapor pressure of isoflurane
$F_V$ = Flow of gas through vaporizer (mL/min)
$F_T$ = Total gas flow (mL/min)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

**Induction:** Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short-acting barbiturate. Inspired concentrations of 1.5 to 3.0% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

**Maintenance:** Surgical levels of anesthesia may be sustained with a 1.0 to 2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5 to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

**HOW SUPPLIED**

FORANE (isoflurane), NDC 10019-360-40, is packaged in 100 mL amber-colored bottles.

**Storage:** Store at room temperature. Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

A-0117

Revised 5-84

**Anaquest** Forane® (isoflurane)

Anaquest
2005 West Beltline Highway
Madison WI 53713 2318
608 273 0019
Telex 910 286 2792
A Division of BOC Inc

Form No. 04-0086-A01

# What would Hippocrates say about brain monitoring?

Throughout history, the arrival of new medical technologies has confronted physicians with new ethical quandaries.

In every case, the basic questions are these: At what point does a new method of treatment cross the line between expensive luxury and standard procedure?

How does one know when the experimental has become the expected?

When does a doctor's obligation to keep abreast of new developments grow into a duty to employ them?

It is precisely these issues that are being addressed today with regard to surgical brain monitoring.

Very few would question the intentions of those who advocate monitoring the brain during cardiovascular and other major surgeries. With reported morbidity rates ranging from the unfortunate to the shocking, something clearly ought to be done. The controversy arises around such issues as cost, ease of use and the effectiveness of the existing technology.

Well, the technology is now remarkably effective. We know; we made it that way.

There is currently available a brain monitor that offers continuous 16-channel (whole-head) EEG data throughout surgery. Thanks to computerization, it requires no special supervision; and it can alert the surgical team immediately when it detects an abnormality in brain function.

Thus, ease of use and effectiveness are no longer prohibitive factors.

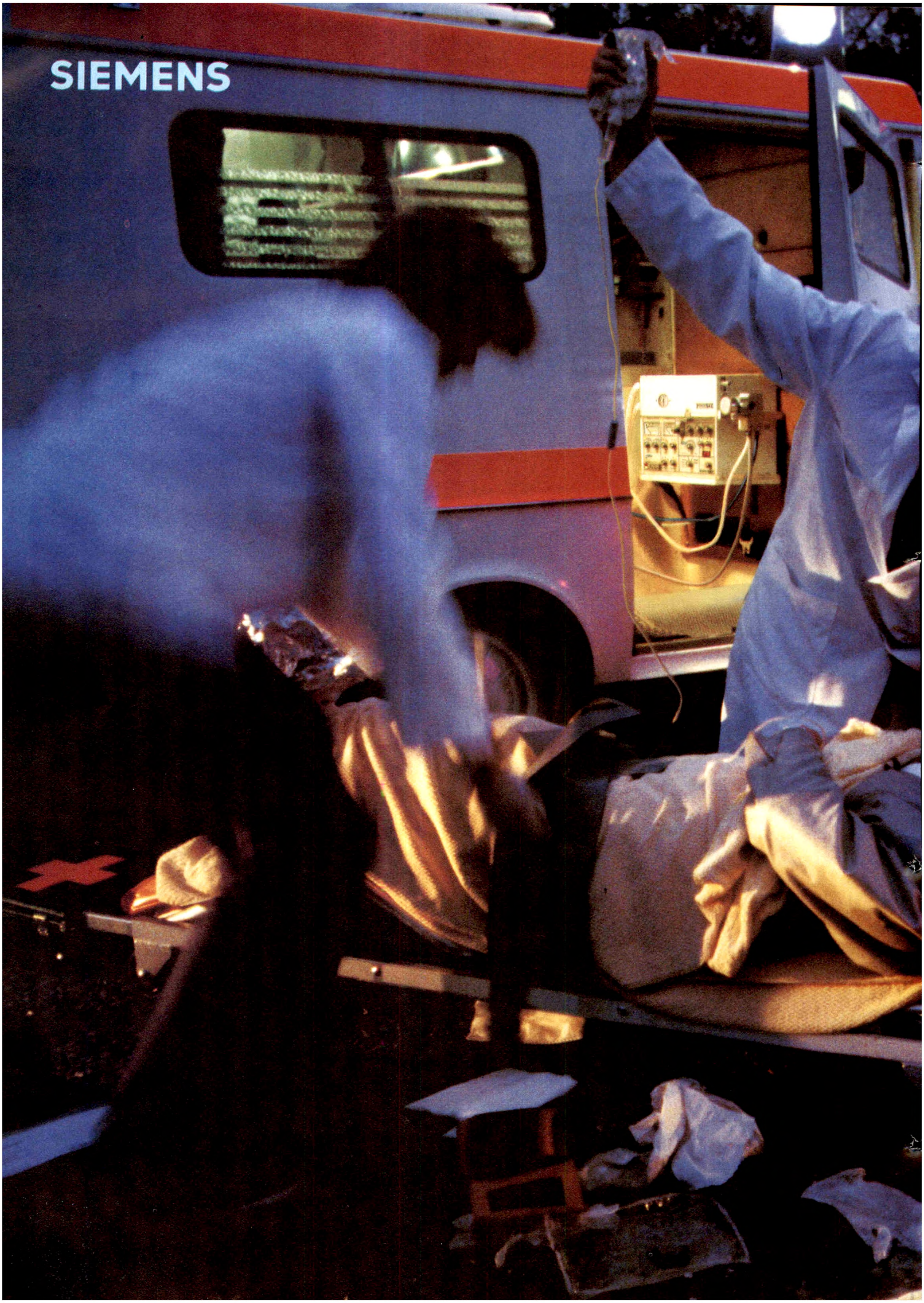
The cost, however, might still be considered an obstacle. And the insurance industry's position on reimbursement is still evolving.

Even so, one thing is certain. Given this new technology, brain monitoring cannot be ignored by the medical community.

We urge you to discuss the pros and cons of brain monitoring with your colleagues.

And we invite you to tell us what you think. Write CNS, Inc., 10349 W. 70th Street, Minneapolis, Minnesota 55344, or call 800-328-8322 ext. 120. If you request, we will be happy to send you more information on brain monitoring.

CNS


SIEMENS

## When safety comes first

The Servo Ventilator will meet the physician's standards. For prematures, children and adults. In intensive care, anesthesia and patient transportation.

The multi-purpose Servo Ventilator from Siemens – the world leader in advanced ventilators.

**Servo Ventilator Systems**

Siemens-Elema Ventilator Systems
2360 North Palmer Drive, Schaumburg, Illinois 60195
Tel.: (312)397-5900

For countries outside the U.S.:
Siemens-Elema AB, Ventilator Division,
S-171 95 Solna, Sweden

Please
☐ send me the Servo application poster
☐ inform me about the Servo in patient transportation
☐ contact me

Name ______________________________

Position ______________________________

Hospital ______________________________

Address ______________________________

______________________________

# Albumin & PPF are no safer or more effective than Hespan®

(hetastarch)

*...they're simply*

©1985 American Critical Care

## As safe as albumin or PPF

In comparative clinical studies, platelet counts, hematocrits, serum fibrinogen levels, prothrombin times (PT), and partial thromboplastin times (PTT) seen with Hespan were comparable to those seen with albumin or plasma protein fraction (PPF).[1,2]

Other studies demonstrate that when any reduction in platelet count or prolongation of PT or PTT does occur with Hespan, no increased bleeding results, even in patients with multiple trauma.[3-5] As with any volume expander, patients should be monitored for excessive hemodilution of coagulant factors or circulatory overload when large volumes are administered.

When Hespan-treated patients were monitored to detect localized or systemic sepsis, there was no evidence of a decrease in their ability to ward off infection or combat an established infection.[5]

Hespan is nonantigenic and, as with blood-derived colloids, any risk of allergic reaction is minimal. Hespan also has a negligible effect on subsequent blood typing or crossmatching.[6]

## As effective as albumin or PPF

Comparative clinical studies have repeatedly demonstrated that Hespan is as effective as albumin or PPF in postoperative myocardial revascularization,[1-3] and hemorrhagic, traumatic, or septic shock.[4,5,7]

No significant differences between Hespan and albumin or PPF were noted in any efficacy parameter.[1-5,7] Hespan effectively maintained colloid osmotic pressure, restored plasma volume, and improved cardiac output and renal function in hypovolemic patients.[1-5,7] And, the volume-expanding effect of a single infusion of Hespan can persist for 24 hours or longer.

## Half the price of albumin or PPF

Hespan offers a potential savings to your hospital of tens of thousands of dollars a year.

*double the price.*

For additional information, contact the Medical Services Department, American Critical Care, 1600 Waukegan Road, McGaw Park, IL 60085. Phone 1-800-323-4980.

**Lifesaving, moneysaving**

**HESPAN®**
**(hetastarch)**

**American Critical Care**

American Hospital Supply Corporation

*Please see references and brief summary of prescribing information on following page.*

**References:** 1. Diehl JT; Lester JL, Cosgrove DM: Clinical comparison of hetastarch and albumin in postoperative cardiac patients. *Ann Thorac Surg 34* (6):674-679, 1982.
2. Moggio RA, Rha CC, Somberg ED, et al: Hemodynamic comparison of albumin and hydroxyethyl starch in postoperative cardiac surgery patients. *Crit Care Med 11* (12):943-945, 1983. 3. Kirklin JK, Lell WA, Kouchoukos NT: Hydroxyethyl starch versus albumin for colloid infusion following cardiopulmonary bypass in patients undergoing myocardial revascularization. *Ann Thorac Surg 37* (1):40-46, 1984.
4. Puri VK, Paidipaty B, White L: Hydroxyethyl starch for resuscitation of patients with hypovolemia and shock. *Crit Care Med 9* (12):833-837, 1981. 5. Shatney CH, Deepika K, Militello PR, et al: Efficacy of hetastarch in the resuscitation of patients with multisystem trauma and shock. *Arch Surg 118*:804-809, 1983. 6. Daniels MJ, Strauss RG, Smith-Floss AM: Effects of hydroxyethyl starch on erythrocyte typing and blood crossmatching. *Transfusion 22* (3):226-228, 1982.
7. Rackow EC, Falk JL, Fein IA, et al: Fluid resuscitation in circulatory shock: A comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. *Crit Care Med 11*(11):839-850, 1983.

**HESPAN®** (hetastarch)

**6% Hetastarch in 0.9% Sodium Chloride Injection**

***CONTRAINDICATIONS***
Hetastarch is contraindicated in patients with severe bleeding disorders or with severe congestive cardiac and renal failure with oliguria or anuria.

***WARNINGS***
Large volumes may alter the coagulation mechanism. Thus, administration of hetastarch may result in transient prolongation of prothrombin, partial thromboplastin and clotting times. With administration of large doses, the physician should also be alert to the possibility of transient prolongation of bleeding time.
Hematocrit may be decreased and plasma proteins diluted excessively by administration of large volumes of hetastarch.
***Usage in Leukapheresis:*** Significant declines in platelet counts and hemoglobin levels have been observed in donors undergoing repeated leukapheresis procedures due to the volume expanding effects of hetastarch. Hemoglobin levels usually return to normal within 24 hours. Hemodilution by hetastarch and saline may also result in 24 hour declines of total protein, albumin, calcium and fibrinogen values.
***Usage in Pregnancy:*** Reproduction studies have been done in mice with no evidence of fetal damage. Relevance to humans is not known since hetastarch has not been given to pregnant women. Therefore, it should not be used in pregnant women, particularly during early pregnancy, unless in the judgment of the physician the potential benefits outweigh the potential hazards.
***Usage in Children:*** No data available pertaining to use in children.
The safety and compatibility of additives have not been established.

***PRECAUTIONS***
The possibility of circulatory overload should be kept in mind. Special care should be exercised in patients who have impaired renal clearance since this is the principal way in which hetastarch is eliminated. Caution should be used when the risk of pulmonary edema and/or congestive heart failure is increased. Indirect bilirubin levels of 0.83 mg% (normal 0.0-0.7 mg%) have been reported in 2 out of 20 normal subjects who received multiple hetastarch infusions. Total bilirubin was within normal limits at all times; indirect bilirubin returned to normal by 96 hours following the final infusion. The significance, if any, of these elevations is not known; however, caution should be observed before administering hetastarch to patients with a history of liver disease.
Regular and frequent clinical evaluation and laboratory determinations are necessary for proper monitoring of hetastarch use during leukapheresis. Studies should include CBC, total leukocyte and platelet counts, leukocyte differential count, hemoglobin, hematocrit, prothrombin time (PT), and partial thromboplastin time (PTT).
Hetastarch is nonantigenic. However, allergic or sensitivity reactions have been reported (see ADVERSE REACTIONS). If such reactions occur, they are readily controlled by discontinuation of the drug and, if necessary, administration of an antihistaminic agent.

***ADVERSE REACTIONS***
The following have been reported: vomiting, mild temperature elevation, chills, itching, submaxillary and parotid glandular enlargement, mild influenza-like symptoms, headaches, muscle pains, peripheral edema of the lower extremities, and anaphylactoid reactions consisting of periorbital edema, urticaria, and wheezing.

***HOW SUPPLIED***
NDC **0094-0037-05-Hespan®** (6% Hetastarch in 0.9% Sodium Chloride Injection) is supplied sterile and nonpyrogenic in 500 ml intravenous infusion bottles.

***CAUTION***
Federal (U.S.A.) law prohibits dispensing without prescription.
Rev: Feb., 1982

Distributed by
**American Critical Care**
American Hospital Supply Corporation
McGaw Park, IL USA 60085

# IARS REVIEW COURSE LECTURES AVAILABLE

____ 1985, 59th Congress—26 Review Course Lectures—$6.00

____ 1984, 58th Congress—24 Review Course Lectures—$6.00

____ 1983, 57th Congress—16 Review Course Lectures—$5.00

____ 1982, 56th Congress—14 Review Course Lectures—$5.00

To:
International Anesthesia Research Society
3645 Warrensville Center Road
Cleveland, Ohio 44122

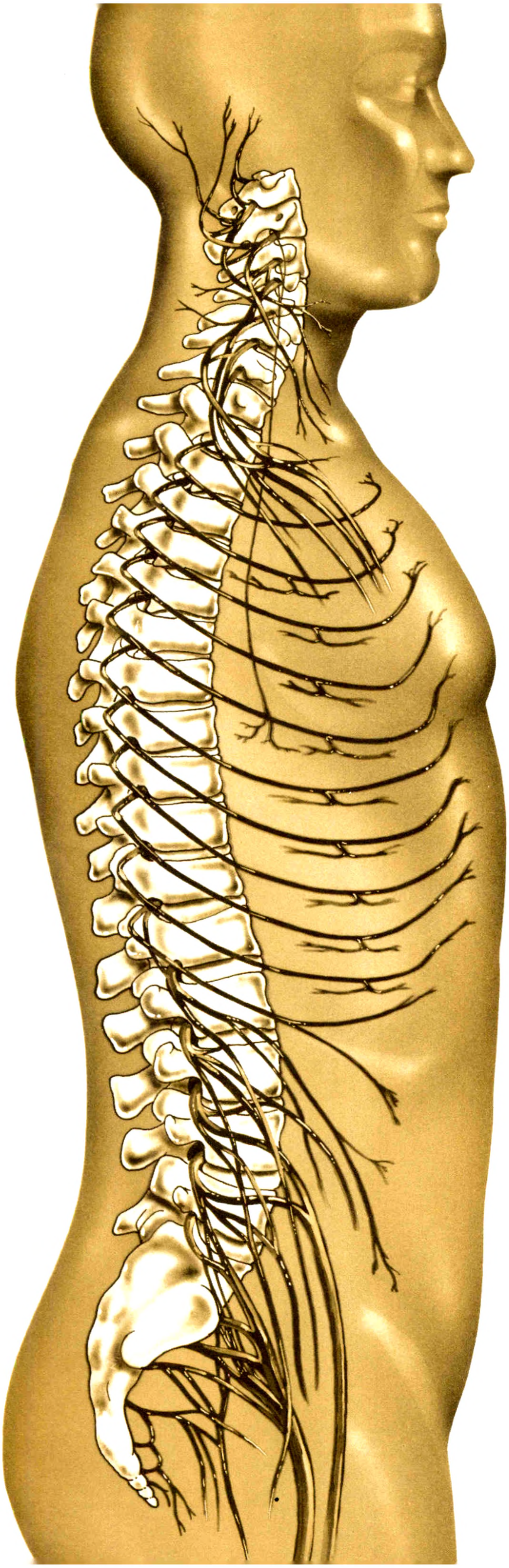
Please send Lecture Booklets checked above.

My check, payable to IARS in the amount of $____________ is enclosed.

(Name)

(Mail Address)

(City, State, Zip)



# Introducing a reliable anesthetic for spinal anesthesia

## Few spinal anesthetic failures

New Marcaine® Spinal offers the advantage of dependable and profound anesthesia for a wide variety of surgical and obstetrical procedures. **MARCAINE** Spinal in a dose of 7.5 mg had only one anesthetic failure in 121 patients.*[1]

## "...reliable local anesthetic solution for spinal anesthesia."[1]

- Rapid onset—within one minute
- Long duration—two to three hours
- Premixed hyperbaric solution
- No added bisulfites

## Marcaine® *Spinal*

(bupivacaine HCl, USP, 0.75% with dextrose, USP, 8.25% injection)

*in a dose of 7.5 mg for perineal and lower extremity surgery

Winthrop-Breon
**WINTHROP-BREON LABORATORIES**
Division of Sterling Drug Inc.
New York, NY 10016

**Reference:**
1. Moore DC: Spinal anesthesia: Bupivacaine compared with tetracaine. *Anesth Analg* 1980; 59:743-750.

©1984 Winthrop-Breon Laboratories

# Marcaine® Spinal

## bupivacaine HCl, USP, 0.75%
## with dextrose, USP, 8.25% injection

**PLEASE CONSULT FULL PRESCRIBING INFORMATION: A SUMMARY FOLLOWS:**

**CONTRAINDICATIONS:** MARCAINE Spinal is contraindicated in patients with a known hypersensitivity to it or to any local anesthetic agent of the amide-type. The following conditions preclude the use of spinal anesthesia: (1) Severe hemorrhage, severe hypotension, or shock and arrythmias, such as complete heart block, which severely restrict cardiac output; (2) Local infection at the site of proposed lumbar puncture; (3) Septicemia.

WARNINGS: LOCAL ANESTHETICS SHOULD ONLY BE EMPLOYED BY CLINICIANS WHO ARE WELL VERSED IN DIAGNOSIS AND MANAGEMENT OF DOSE-RELATED TOXICITY AND OTHER ACUTE EMERGENCIES WHICH MIGHT ARISE FROM THE BLOCK TO BE EMPLOYED, AND THEN ONLY AFTER INSURING THE **IMMEDIATE** AVAILABILITY OF OXYGEN, OTHER RESUSCITATIVE DRUGS, CARDIOPULMONARY RESUSCITATIVE EQUIPMENT, AND THE PERSONNEL RESOURCES NEEDED FOR PROPER MANAGEMENT OF TOXIC REACTIONS AND RELATED EMERGENCIES. (See also ADVERSE REACTIONS and PRECAUTIONS.) DELAY IN PROPER MANAGEMENT OF DOSE-RELATED TOXICITY, UNDERVENTILATION FROM ANY CAUSE AND/OR ALTERED SENSITIVITY MAY LEAD TO THE DEVELOPMENT OF ACIDOSIS, CARDIAC ARREST, AND, POSSIBLY, DEATH.

Spinal anesthetics should not be injected during uterine contractions, because spinal fluid current may carry the drug further cephalad than desired.

A free flow of cerebrospinal fluid while performing spinal anesthesia indicates entry into the subarachnoid space. Aspiration should be performed before the anesthetic is injected to confirm entry into the subarachnoid space and to avoid intravascular injection.

MARCAINE solutions containing epinephrine or other vasopressors should not be used concomitantly with ergot-type oxytocic drugs, because severe, persistent hypertension may occur. MARCAINE solutions containing a vasoconstrictor such as epinephrine should be used cautiously in patients receiving monoamine oxidase inhibitors (MAOI) or antidepressants of the triptyline or imipramine types, because severe prolonged hypertension may result.

Administration of MARCAINE to patients younger than 18 years is not recommended, nor is the mixing or the prior or intercurrent use of any other local anesthetic with MARCAINE because of insufficient data on the clinical use of such mixtures.

**PRECAUTIONS: General:** The safety and effectiveness of spinal anesthetics depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Resuscitative equipment, oxygen, and other resuscitative drugs should be available for immediate use. (See WARNINGS and ADVERSE REACTIONS.) The patients should have IV fluids running via an indwelling catheter to assure a functioning intravenous pathway. The lowest dosage of local anesthetic that results in effective anesthesia should be used. Aspiration for blood should be performed before injection and injection should be made slowly. Tolerance varies with the status of the patient. Elderly patients and acutely ill patients may require reduced doses. Reduced doses may also be indicated in patients with increased intra-abdominal pressure (including obstetrical patients), if otherwise suitable for spinal anesthesia.

Cardiovascular and respiratory vital signs and the patient's state of consciousness after local anesthetic injection should be constantly and carefully monitored. Restlessness, anxiety, incoherent speech, light-headedness, numbness, and tingling of the mouth and lips, metallic taste, tinnitus, dizziness, blurred vision, tremors, depression or drowsiness may be early warning signs of central nervous system toxicity.

Spinal anesthetics should be used cautiously in patients with severe disturbances of cardiac rhythm, shock or heart block.

Sympathetic blockade during spinal anesthesia may result in peripheral vasodilation and hypotension, the extent depending on the number of dermatomes blocked. Blood pressure should be carefully monitored especially in the early phases of anesthesia. Hypotension may be controlled by vasoconstrictors in dosages depending on the severity of hypotension and response of treatment. The level of anesthesia should also be carefully monitored because it is not always controllable in spinal techniques.

Because the liver metabolizes amide-type local anesthetics such as MARCAINE, these drugs, especially repeat doses, should be used cautiously in patients with hepatic disease. Patients with severe hepatic disease are at a greater risk of developing toxic plasma concentrations. Local anesthetics should also be used cautiously in patients with impaired cardiovascular function because they may be less able to compensate for functional changes associated with the prolongation of A-V conduction produced by these drugs. However, dosage recommendations for spinal anesthesia are much lower than those in other major blocks; most experience regarding hepatic and cardiovascular disease dose-related toxicity is derived from these other major blocks.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are used in patients during or following the administration of potent inhalation agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents on the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be considered.

Many drugs used during the conduct of anesthesia are considered potential triggering agents for familial malignant hyperthermia. It is not known whether amide-type local anesthetics trigger this reaction, and since the need for supplemental general anesthesia cannot be predicted in advance, a standard protocol for management should be available. Early unexplained signs of tachycardia, tachypnea, labile blood pressure, and metabolic acidosis may precede temperature elevation. Successful outcome depends on early diagnosis, prompt discontinuance of the suspect triggering agent(s) and institution of treatment, including oxygen therapy, indicated supportive measures and dantrolene. (Consult dantrolene sodium package insert before using.)

The following conditions may preclude the use of spinal anesthesia, depending on the physician's evaluation of the situation and ability to deal with possible complications or complaints: (1) Preexisting diseases of the central nervous system, such as those resulting from pernicious anemia, poliomyelitis, syphilis, tumor; (2) Hematological disorders predisposing to coagulopathies or patients on anticoagulant therapy. Trauma to a blood vessel during the conduct of spinal anesthesia may, in some instances, result in uncontrollable central nervous system hemorrhage or soft tissue hemorrhage; (3) Chronic backache and preoperative headache; (4) Hypotension and hypertension; (5) Technical problems (persistent paresthesias or bloody tap); (6) Arthritis or spinal deformity; (7) Extremes of age; (8) Psychosis or other causes of poor cooperation by the patient.

**Information for Patients:** Patients should be informed that they may experience temporary loss of sensation and motor activity, usually in the lower half of the body, following proper administration of spinal anesthesia. Also, when appropriate, the physician should discuss other information including adverse reactions in the MARCAINE Spinal package insert.

**Clinically Significant Drug Interactions:** Local anesthetic solutions containing epinephrine or norepinephrine administered to patients receiving monoamine oxidase inhibitors or tricyclic antidepressants may produce severe, prolonged hypertension. Concurrent use of these agents should generally be avoided but, when necessary, careful patient monitoring is essential.

Concurrent administration of vasopressor drugs and of ergot-type oxytocic drugs may cause severe persistent hypertension or cerebrovascular accidents.

Phenothiazines and butyrophenones may reduce or reverse the pressor effect of epinephrine.

**Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Long-term studies in animals of most local anesthetics including bupivacaine to evaluate carcinogenic potential have not been conducted. Mutagenic potential or the effect on fertility have not been determined. There is no evidence from human data that MARCAINE Spinal may be carcinogenic, or mutagenic or that it impairs fertility.

**Pregnancy Category C:** Decreased pup survival in rats and an embryocidal effect in rabbits have been observed when bupivacaine hydrochloride was administered in doses comparable to 230 and 130 times respectively the maximum recommended human spinal dose. There are no adequate and well-controlled studies in pregnant women of bupivacaine's effect on the developing fetus. Bupivacaine hydrochloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. This does not exclude the use of MARCAINE Spinal at term for obstetrical anesthesia. (See **Labor and Delivery.**)

**Labor and Delivery:** Spinal anesthesia has a recognized use during labor and delivery. Bupivacaine hydrochloride, when administered properly, via the epidural route in doses 10 to 12 times the amount used in spinal anesthesia has been used for obstetrical analgesia and anesthesia without evidence of adverse effects on the fetus.

Regional anesthesia has produced maternal hypotension. Local anesthetics produce vasodilation by blocking sympathetic nerves. Elevating the patient's legs and positioning her on her left side will help prevent decreases in blood pressure. The fetal heart rate should be monitored continuously and electronic fetal monitoring is highly advisable.

It is extremely important to avoid aortocaval compression by the gravid uterus during administrations of regional block to parturients. To do this, the patient must be maintained in the left lateral decubitus position or a blanket roll or sandbag may be placed beneath the right hip and the gravid uterus displaced to the left.

Spinal anesthesia may alter the forces of parturition through changes in uterine contractility or maternal expulsive efforts. Spinal anesthesia has also been reported to prolong the second stage of labor by removing the parturient's reflex urge to bear down or by interfering with motor function. Obstetrical anesthesia may increase the need for forceps assistance.

The use of some local anesthetic drug products during labor and delivery may result in diminished muscle strength and tone for the first day or two of life. This has not been reported with bupivacaine.

Cardiac arrest has been reported during use of MARCAINE 0.75% solution for epidural anesthesia in obstetrical patients. The MARCAINE hydrochloride package insert for epidural, nerve block, etc, discusses this problem. These cases are compatible with systemic toxicity following unintended intravascular injection of the much larger doses recommended for epidural anesthesia and have not occurred within the dose range of bupivacaine hydrochloride 0.75% recommended for obstetrical spinal anesthesia. The 0.75% concentration of MARCAINE is therefore not recommended for obstetrical epidural anesthesia. MARCAINE Spinal (bupivacaine HCl 0.75% with dextrose 8.25%) is recommended for spinal anesthesia in obstetrics.

**Nursing Mothers:** It is not known whether local anesthetic drugs are excreted in human milk; therefore, caution should be exercised when local anesthetics are administered to a nursing woman.

**Pediatric Use:** Until further experience is gained in patients younger than 18 years, administration of MARCAINE Spinal in this age group is not recommended.

**ADVERSE REACTIONS:** Reactions to bupivacaine are characteristic of those associated with other amide-type local anesthetics. The most commonly encountered acute adverse experiences following spinal anesthesia are hypotension due to loss of sympathetic tone and respiratory paralysis or underventilation due to cephalad extension of the motor level of anesthesia. These may lead to cardiac arrest if untreated. In addition, dose-related convulsions and cardiovascular collapse may result from diminished tolerance, rapid absorption from the injection site, or from unintentional intravascular injection of a local anesthetic solution. Factors influencing plasma protein binding, such as acidosis, systemic diseases which alter protein production, or competition of other drugs for protein binding sites, may diminish individual tolerance.

**Respiratory System:** Respiratory paralysis or underventilation may result from upward extension of the level of spinal anesthesia and may lead to secondary hypoxic cardiac arrest if untreated. Preanesthetic medication, intraoperative analgesics and sedatives, as well as surgical manipulation may contribute to underventilation. This will usually occur within minutes of the injection of spinal anesthetic solution, but because of differing maximal onset times, intercurrent drug use, and surgical manipulation, it may occur at any time during surgery or the immediate recovery period.

**Cardiovascular System:** Hypotension due to loss of sympathetic tone is a commonly encountered extension of the clinical pharmacology of spinal anesthesia. This is more commonly observed in patients with shrunken blood and interstitial fluid volumes, cephalad spread of the local anesthetic and/or mechanical obstruction of venous return. Nausea and vomiting are frequently associated with hypotensive episodes following the administration of spinal anesthesia. High doses, or inadvertent intravascular injection, may lead to high plasma levels and related depression of the myocardium, decreased cardiac output, bradycardia, heart block, ventricular arrhythmias and possibly cardiac arrest. (See WARNINGS, PRECAUTIONS, and OVERDOSAGE sections.)

**Central Nervous System:** Respiratory paralysis or underventilation secondary to cephalad spread of the level of spinal anesthesia (see Respiratory System) and hypotension for the same reason (see Cardiovascular System) are the two most commonly encountered central nervous system-related adverse observations which demand immediate countermeasures.

High doses, or inadvertent intravascular injections may lead to high plasma levels and related central nervous system toxicity characterized by excitement and/or depression. Restlessness, anxiety, dizziness, tinnitus, blurred vision, or tremors may occur, possibly proceeding to convulsions. However, excitement may be transient or absent, with depression being the first manifestation of an adverse reaction. This may quickly be followed by drowsiness merging into unconsciousness and respiratory arrest.

**Neurologic:** Adverse neurologic reactions associated with the use of local anesthetics may be related to the total dose of local anesthetic administered and also depend on the particular drug used, the route of administration and the physical status of the patient. Many effects may be related to local anesthetic techniques, with or without a contribution from the drug.

Neurologic effects following spinal anesthesia may include loss of perineal sensation and sexual function; persistent anesthesia, paresthesia, weakness and paralysis of the lower extremities and loss of sphincter control all of which may have slow, incomplete or no recovery; hypotension; high or total spinal block; urinary retention; headache; backache; septic meningitis; meningismus; arachnoiditis; slowing of labor, increased incidence of forceps delivery; shivering; cranial nerve palsies due to traction on nerves from loss of cerebrospinal fluid; fecal and urinary incontinence.

**Allergic:** Allergic-type reactions are rare and may occur as a result of sensitivity to the local anesthetic. These reactions include urticaria, pruritus, erythema, angioneurotic edema (including laryngeal edema), tachycardia, sneezing, nausea, vomiting, dizziness, syncope, excessive sweating, elevated temperature, and possibly anaphylactoid-like symptomatology (including severe hypotension). Cross-sensitivity among members of the amide-type local anesthetic group has been reported.

**Other:** Nausea and vomiting may occur during spinal anesthesia.

**OVERDOSAGE:** Acute emergencies from local anesthetics are generally related to high plasma levels encountered during therapeutic use or to underventilation (and perhaps apnea) secondary to upward extension of spinal anesthesia. Hypotension is commonly encountered during the conduct of spinal anesthesia due to relaxation of sympathetic tone or contributory mechanical obstruction of venous return.

**Management of Local Anesthetic Emergencies:** The first consideration is prevention through careful and constant monitoring of cardiovascular and respiratory vital signs and the patient's state of consciousness after each local anesthetic injection. Administer oxygen at the first sign of change.

*The first step in managing systemic toxic reactions, as well as underventilation or apnea due to a high or total spinal is to* ***immediately*** *establish and maintain a patent airway and effective assisted or controlled ventilation with 100% oxygen with a delivery system capable of permitting immediate positive airway pressure by mask.* This may prevent convulsions if they have not already occurred.

If necessary, use drugs to control convulsions. A 50 mg to 100 mg bolus IV injection of succinylcholine will paralyze the patient without depressing central nervous or cardiovascular systems and facilitate ventilation. A bolus IV dose of 5 mg to 10 mg of diazepam or 50 mg to 100 mg of thiopental will permit ventilation and counteract central nervous system stimulation, but these drugs also depress central nervous system, respiratory and cardiac function, add to postictal depression and may result in apnea. Intravenous barbiturates, anticonvulsant agents, or muscle relaxants should only be administered by those familiar with their use. Immediately after instituting these ventilatory measures, the adequacy of the circulation should be evaluated. Supportive treatment of circulatory depression may require administration of intravenous fluids, and when appropriate, a vasopressor dictated by the clinical situation.

Hypotension due to sympathetic relaxation may be managed with intravenous fluids, in an attempt to relieve mechanical obstruction of venous return or by using vasopressors and, if indicated, by giving plasma expanders or whole blood.

Endotracheal intubation, employing drugs and techniques familiar to the physician, may be indicated after initial administration of oxygen by mask if difficulty is encountered in maintaining a patent airway or if prolonged ventilatory (assisted or controlled) support is indicated.

Recent clinical data from patients experiencing local anesthetic-induced convulsions demonstrated rapid development of hypoxia, hypercarbia, and acidosis with bupivacaine within a minute of the onset of convulsions. These observations suggest that oxygen consumption and carbon dioxide production are greatly increased during local anesthetic convulsions and emphasize the importance of immediate and effective ventilation with oxygen which may avoid cardiac arrest.

If not treated immediately, convulsions with simultaneous hypoxia, hypercarbia, and acidosis plus myocardial depression from the direct effects of the local anesthetic may result in cardiac arrhythmias, bradycardia, asystole, ventricular fibrillation, or cardiac arrest. Respiratory abnormalities, including apnea, may occur. Underventilation or apnea due to a high or total spinal may produce these same signs and also lead to cardiac arrest if ventilatory support is not instituted. If cardiac arrest occurs, standard cardiopulmonary resuscitative measures should be instituted and maintained for a prolonged period if necessary. Recovery has been reported after prolonged resuscitative efforts.

The supine position is dangerous in pregnant women at term because of aortocaval compression by the gravid uterus. Therefore, during treatment of systemic toxicity, maternal hypotension or fetal bradycardia following regional block, the parturient should be maintained in the left lateral decubitus position if possible, or manual displacement of the uterus off the great vessels be accomplished.

The mean seizure dosage of bupivacaine in rhesus monkeys was found to be 4.4 mg/kg with mean arterial plasma concentration of 4.5 mcg/mL. The intravenous and subcutaneous $LD_{50}$ in mice is 6 mg/kg to 8 mg/kg and 38 mg/kg to 54 mg/kg respectively.

**Composition of MARCAINE Spinal Solutions:** Each 1 mL of MARCAINE Spinal contains 7.5 mg bupivacaine hydrochloride and 82.5 mg dextrose. The pH of this solution is adjusted between 4.0 and 6.5 with sodium hydroxide or hydrochloric acid. The specific gravity of MARCAINE Spinal is between 1.030 and 1.035 at 25°C, and 1.03 at 37°C. MARCAINE Spinal does not contain any preservatives.

Winthrop-Breon

**WINTHROP-BREON LABORATORIES**
Division of Sterling Drug Inc.
New York, NY 10016

ANESTH ANALG
1985;64:1137–42

# Blunting of Stress Responses in the Pulmonary Circulation of Infants by Fentanyl

Paul R. Hickey, MD, Dolly D. Hansen, MD, David L. Wessel, MD, Peter Lang, MD, Richard A. Jonas, MD, and E. Marsha Elixson, RN, BNS

HICKEY PR, HANSEN DD, WESSEL DL, LANG P, JONAS RA, ELIXSON EM. Blunting of stress responses in the pulmonary circulation of infants by fentanyl. Anesth Analg 1985;64:1137–42.

*After repair of congenital heart defects, stress responses in the pulmonary circulation of fourteen infants produced by a brief endotracheal suctioning procedure were studied before and after fentanyl (25 μg/kg). The total time of disconnection from the ventilator with suctioning ($F_{IO_2}$ 1.0) was limited to no more than 15 sec to avoid alveolar hypoxia. Before fentanyl, marked increases occurred in mean pulmonary artery pressure and pulmonary vascular resistance index with suctioning, whereas only mild increases in heart rate and mean systemic arterial pressure occurred. All of these increases with suctioning were almost completely abolished by 25 μg/kg fentanyl. We conclude that suctioning or other broncho–carinal stimulation can produce a marked pulmonary vasoconstrictive response in infants, which is blunted by fentanyl. This response is separate from that produced by hypoxic pulmonary vasoconstriction associated with prolonged clinical suctioning procedures or with loss of airway.*

Key Words: ANALGESICS—fentanyl. ANESTHESIA, CARDIOVASCULAR—pediatric. LUNG—vasculature.

Although the blunting of stress-induced responses in the systemic circulation has been studied extensively, stress-induced changes in the pulmonary circulation have received little attention. Changes in the pulmonary circulation are particularly critical in neonates whose pulmonary vasculature is highly reactive, in children with congenital heart disease, and in adult patients with pulmonary hypertension from diverse causes. During anesthesia and operation, there is potential for dynamic and potentially deleterious changes in the pulmonary circulation due to stress of airway manipulations, alterations in inspired gas tensions, and surgical trauma.

Previous studies from this institution have demonstrated that fentanyl in large doses produces little alteration in either pulmonary or systemic hemodynamics of infants; that it attenuates the systemic hemodynamic response to intubation, incision, and sternotomy; and that it contributes to stability of the pulmonary circulation in neonates after repair of congenital diaphragmatic hernia (1–3). No studies of the effects of fentanyl on the pulmonary circulation in infants during stress have been reported.

To investigate the effects of stress on the pulmonary circulation in infants, we used, as a stress stimulus, a modification of the endotracheal suctioning procedure routinely employed during postoperative clinical care. Although a number of studies have documented increases in heart rate and systemic arterial pressure both with endotracheal suctioning and during broncho–carinal stimulation without suctioning (4–7), the effects of this stress on the pulmonary circulation have not been assessed, either in the awake patient or after a large dose of fentanyl. Because of the crucial role of the pulmonary circulation in sick infants and because of the hemodynamic complications seen clinically during endotracheal suctioning in infants, we designed our study to assess the effects of the stress of endotracheal stimulation without alveolar hypoxia on the pulmonary circulation of infants before and after fentanyl.

## Methods

The study protocol was approved by the institutional Committee on Clinical Investigation, and informed

---

Supported in part by the CHMC Anesthesia Foundation, Inc. Presented in part at the ASA Annual Meeting 1984.

Received from the Departments of Anesthesia, Cardiology, and Cardiovascular Surgery, The Children's Hospital and Harvard Medical School, Boston, Massachusetts. Accepted for publication June 24, 1985.

Address correspondence to Dr. Hickey, Department of Anesthesia, The Children's Hospital, 300 Longwood Avenue, Boston, MA 02115.

© 1985 by the International Anesthesia Research Society

consent was obtained from the parents of the infants included in the study. We studied 14 infants when they were responsive in the intensive care unit after operative repair of congenital heart defects. Mean age was 7 months (± 2.7 SD), and mean weight was 6.1 kg (± 1.5). Operative procedures included closure of ventricular septal defects (4), repair of complete atrioventricular canals (6), repair of tetralogies of Fallot (2), Senning repair of transposition of the great arteries (1), and mitral valve replacement (1).

Only hemodynamically stable infants not requiring inotropic support were studied. Indwelling right and left atrial, pulmonary artery, and radial artery catheters were inserted during the operation, along with a separate pulmonary artery thermistor. Postoperative chest x-rays and pressure tracings confirmed the position of the intrathoracic catheters. Pulmonary arterial oxygen saturations of less than 80% or normal indocyanine green dye studies confirmed the absence of residual intracardiac shunts.

All infants had received approximately 50 μg/kg of fentanyl for anesthesia prior to cardiopulmonary bypass and subsequent deep hypothermic circulatory arrest; no further fentanyl was given until the time of the study in the intensive care unit. The infants were being mechanically ventilated with an $FI_{O_2}$ of 1.0 during the study, which was generally 5–7 hr after the operation. Baseline mean arterial blood pH for the group was 7.48 ± 0.04 (SD), mean $PaCO_2$ was 37 ± 5 mm Hg, and the mean $PaO_2$ was 210 ± 35 mm Hg.

Baseline measurements of left and right atrial, mean pulmonary, and systemic arterial pressures were made, and a thermodilution cardiac output was determined by injecting either 1 or 3 ml of 5% dextrose solution (0° C) through the right atrial catheter. The volume of injectate depended upon the infant's weight. Thermodilution curves were examined, and three determinations of cardiac output were obtained for each measurement period. Successive cardiac output determinations were generally within 5% of each other and always within 10%.

After baseline measurements on an $FI_{O_2}$ of 1.0, the infants were suctioned to a measured depth of the tracheobronchial tree. Interruption of ventilation with this suctioning maneuver was limited to less than 15 sec, after which controlled ventilation with 100% $O_2$ was continued. In half of the infants, transcutaneous $PO_2$ monitors were in place during the period of suctioning, and no decrease in transcutaneous $PO_2$ was noted with the brief, carefully controlled suctioning technique used. Hemodynamic responses to endotracheal suctioning generally lasted several minutes and returned to baseline levels within 5–10 min. Maximum responses of pressure and heart rate to suctioning were recorded, and repeat measurements of thermodilution cardiac output were done as closely as possible to the time of the maximum pressure responses.

The suctioning technique used for this study was much briefer and more limited than the prolonged suctioning technique used clinically. Clinical suctioning procedures generally include instillation of saline, a number of passes of the suction catheter with longer periods of suction on each pass, and longer periods of disconnection from ventilation than the brief technique used in this investigation. Because the aim of this study was to examine responses to stimulation of the tracheobronchial tree rather than hypoxic pulmonary vasoconstriction, this brief suctioning technique was used purposely to avoid alveolar hypoxia and concomitant hypoxemia, which have been reported with usual clinical suctioning techniques.

After the first suctioning, fentanyl (25 μg/kg) was given intravenously over 1–2 min along with a small dose of pancuronium to prevent rigidity (0.015 mg/kg). The hemodynamic effects of fentanyl and pancuronium in these infants have been reported in a previous paper (1). The above sequence of measurements, including new baseline measurements, was repeated 10 min after the full dose of fentanyl. Endotracheal suctioning of less than 15 sec duration was then again carried out to the same depth as on the first occasion and the measurements repeated. In four infants the endotracheal suction catheter was passed to the measured depth to provide broncho–carinal stimulation, but no suction was applied either before or after fentanyl.

All hemodynamic indices were calculated for each infant using body surface areas derived from a computer program based upon height and weight. Cardiac index (CI) and pressure data were used to calculate pulmonary vascular resistance index (PVRI) and systemic vascular resistance index (SVRI) in Wood units ($mm\ Hg \cdot L^{-1} \cdot min \cdot m^2$) for each infant. Group mean values and standard deviations (SD) for each variable were calculated directly. One way analysis of variance (ANOVA) for repeated measures was used for the raw data to determine whether significant differences occurred among the four measurement periods (baseline, suctioning before fentanyl, baseline after fentanyl, and suctioning after fentanyl). When significance was noted, the Bonferroni *t*-test for multiple comparisons was used to test the significance of changes occurring between baseline and initial suctioning before fentanyl and also between suctioning before fentanyl and suctioning after fentanyl. A $P$ value of $< 0.05$ was considered statistically significant.

In order to compare suctioning-related changes in

Table 1. Hemodynamic Stress Responses to Suctioning Before and After Fentanyl (± SD)

| Variable | Baseline | Suctioning response before fentanyl | Baseline after fentanyl | Suctioning response after fentanyl |
|---|---|---|---|---|
| Heart rate (beats/min) | 113 ± 17 | 124 ± 22[a] | 115 ± 18 | 114 ± 17[b] |
| MAP (mm Hg) | 72 ± 13 | 88 ± 16[a] | 70 ± 15 | 72 ± 15[b] |
| RAP (mm Hg) | 8 ± 3 | 17 ± 11[a] | 10 ± 3 | 11 ± 5[c] |
| MPAP (mm Hg) | 21 ± 8 | 36 ± 13[a] | 21 ± 7 | 23 ± 7[b] |
| LAP (mm Hg) | 12 ± 5 | 20 ± 10[a] | 12 ± 4 | 14 ± 4[c] |
| Cardiac index (L·min·m$^2$) | 2.8 ± 0.6 | 3.1 ± 0.7 | 3.0 ± 0.6 | 2.9 ± 0.6 |
| SVRI (mm Hg·L$^{-1}$·min·m$^2$) | 24 ± 7 | 24 ± 8 | 21 ± 7 | 23 ± 9 |
| PVRI (mm Hg·L$^{-1}$·min·m$^2$) | 3.3 ± 2.0 | 5.6 ± 3.5[a] | 3.1 ± 2.1 | 3.3 ± 2.2[b] |

[a] $P < 0.01$ Compared to baseline.
[b] $P < 0.01$ Compared to suctioning response before fentanyl.
[c] $P < 0.05$ Compared to suctioning response before fentanyl.

each variable before and after fentanyl, the percent change in each hemodynamic variable with suctioning was calculated from the immediately preceding baseline period both before and after fentanyl for each infant. New baseline measurements were made after fentanyl was given and used in the calculation of the percent change with suctioning after fentanyl. To provide another view of the data, mean percent changes with suctioning before and after fentanyl were compared by the Student's paired *t*-test.

## Results

In the four patients who received only broncho–carinal stimulation with the catheter, the resulting response was no different from the 10 patients in whom brief suction was applied to the catheter. Accordingly, data from all 14 infants were pooled for subsequent analysis. The hemodynamic responses of these 14 infants to broncho–carinal stimulation with or without suctioning before fentanyl and after fentanyl are shown in Table 1.

Heart rate (HR) and systemic arterial pressure (MAP) increased moderately with suctioning before fentanyl; these increases were statistically significant. Larger increases occurred in pulmonary arterial pressure (MPAP) and PVRI. Cardiac index and SVRI tended to increase slightly with suctioning, but the changes were not statistically significant. Right atrial pressure (RAP) and left atrial pressure (LAP) increased significantly by similar amounts with suctioning (9 and 8 mm Hg, respectively). The increase in MPAP (15 mm Hg) was almost two times the increase in the RAP and the LAP, whereas CI was unchanged, suggesting that the increase in MPAP was not due merely to increased intrathoracic pressure with straining during broncho–carinal stimulation.

After fentanyl had been given, the responses to suctioning were significantly different. Heart rate, MAP, RAP, MPAP, LAP, and PVRI responses to suctioning all were significantly decreased by fentanyl when compared to suctioning responses before fentanyl was given. There was no change in the minimal CI and SVRI responses to suctioning after fentanyl.

Figures 1 and 2 show the mean percent changes in each variable for the entire group with endotracheal suctioning compared before and after fentanyl. There was a significant decrease in the percent hemodynamic response to suctioning after fentanyl in HR, MAP, MPAP, and PVRI. Although the percent change in CI with suctioning before fentanyl was insignificant, the CI response was significantly different after fentanyl. This is because CI decreased with suctioning after fentanyl when the heart rate response to suctioning was blunted by fentanyl.

The most striking stress response with suctioning was produced in the pulmonary circulation. This pulmonary vascular response was markedly attenuated by fentanyl. As indicated by the high relative standard deviations in the MPAP and PVRI data (Table 1), the pulmonary vascular response to suctioning was quite variable before fentanyl. Some infants had large increases in MPAP with suctioning prior to fentanyl; others had only mild or moderate increases. Regardless of the magnitude of the response prior to fentanyl, the pulmonary vascular response was quite uniformly blunted, as shown by the lower standard deviations in these data after fentanyl.

## Discussion

Significant hemodynamic changes occurred with suctioning in the infants we studied; these changes were especially marked in the pulmonary circulation. Because there is only limited information in the literature concerning the effects of acute hypertensive responses in the pulmonary circulation, it is difficult to assess the clinical importance of the changes we ob-

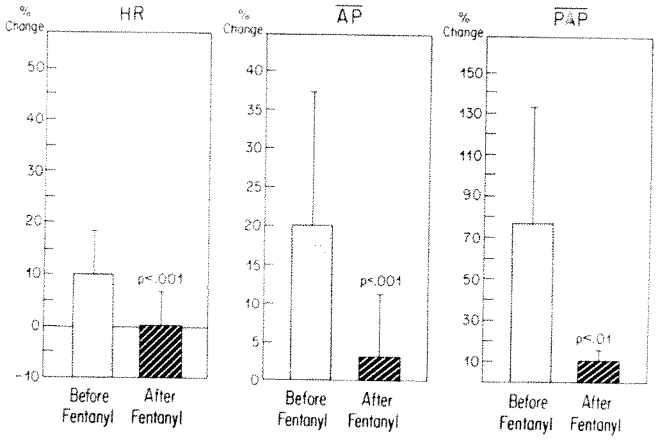


Figure 1. Percent changes in heart rate (HR), mean arterial pressure (AP), and mean pulmonary arterial pressure (PAP) with endotracheal suctioning before and after fentanyl.

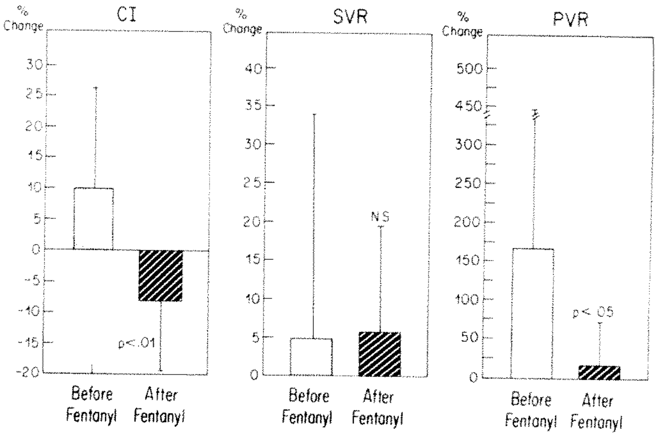


Figure 2. Percent changes in cardiac index (CI), systemic vascular resistance index (SVR), and pulmonary vascular resistance index (PVR) with endotracheal suctioning before and after fentanyl.

served. Acute right ventricular failure secondary to pulmonary vasoconstriction in adults given protamine has recently been documented (8). In infants, hemodynamic complications associated with suctioning are well known to occur clinically (9), and death has been reported after endotracheal suctioning in adults (10). When coupled to the pulmonary vasoconstrictive response associated with brief stimulation of the tracheobronchial tree demonstrated in the present study, the hypoxia often produced in young infants during prolonged therapeutic suctioning and saline instillation procedures (9) could very likely lead to additional pulmonary vasoconstriction mediated by alveolar hypoxia. Acute right ventricular failure might result. After repair of congenital diaphragmatic hernias in neonates, stress-related pulmonary vasoconstrictive responses have been shown to be critically related to right-to-left shunting and systemic hypoxemia (3). Furthermore, other forms of sympathomimetic stress such as potent surgical stimulation may also provoke similar responses in the pulmonary circulation.

Previous studies have documented systemic hemodynamic effects of endotracheal suctioning and broncho–carinal stimulation similar to those seen in the present study but did not evaluate changes in pulmonary arterial pressures or pulmonary vascular resistance. White et al. (7) showed that 1 $\mu$g/kg of fentanyl did not prevent heart rate and systemic pressor responses to endotracheal suctioning. Martin et al. (11) showed that in adults fentanyl 8 $\mu$g/kg added to the thiopental blunts both systemic response to tracheal intubation and the increase in pulmonary capillary wedge pressure associated with tracheal intubation. Pulmonary arterial pressures were not reported in their study. Other studies in which patients' pulmonary vascular responses to stress have been measured incidentally after fentanyl administration have not included any baseline measurements of responses to stress before fentanyl. Thus these studies do not allow quantitation of the degree of attenuation of the pulmonary vascular stress response (12–13). In a study by Wynands et al. (12) of adults undergoing coronary artery bypass grafting receiving fentanyl, there was no significant change in PVR with incision and sternotomy. Calculation of PVRI from the study by Sonntag et al. (13) of adults given fentanyl shows an apparent increase in PVRI with the stress of intubation but not with incision and sternotomy.

In the present study, the variability in the vascular response to suctioning was greater in the pulmonary than in the systemic circulation, as indicated by the larger relative standard deviations in the pulmonary data. Some of this variability may be related to intrinsic differences in the pulmonary vascular responsiveness to broncho–carinal stimulation among different infants. In our study these individual differences were not clearly related to age, diagnosis, level of pulmonary vascular resistance, or preexisting pulmonary hypertension (six infants), but the number of infants studied was too small to allow any valid conclusion on this point. Furthermore, because both the amount of sedation the infants received prior to the study and the time interval after operation were not strictly controlled, different preexisting levels of sedation during the measurement made before fentanyl administration might also contribute to the observed variability.

The greater variability of the PVRI data with suctioning may also be explained partially by the transient nature of the response to suctioning and our inability to measure cardiac output instantaneously.

The suctioning response typically lasted several minutes, and hemodynamic values returned to baseline within 5-10 min. Although maximal pressure responses could be measured with no time lag, a series of thermodilution output measurements takes several minutes. Thus during this non-steady state we would expect that appreciable variability in the PVRI (and SVRI) data to be introduced because of the time lag between pressure measurements and cardiac output measurements. Despite this variability, changes in PVRI associated with suctioning still attained statistical significance.

These considerations of course do not apply to the immediate measurement of MPAP, which still showed a moderately large degree of variability among infants. Whether this apparent variability in responsiveness of the pulmonary vasculature is an artifact of our study design or whether it represents an intrinsic biologic variability in different infants is an interesting question raised by this study.

Hypoxic pulmonary vasoconstriction is an unlikely explanation for our results because the brief suctioning technique was purposely used to avoid producing alveolar hypoxia. Suctioning time was minimal, less than 5 sec, interrupting ventilation for less than 15 sec, and transcutaneous $P_{O_2}$ showed no change during suctioning. In comparison, the usual clinical suctioning techniques frequently involve a total ventilator disconnect time of several minutes, with saline being instilled, and several suctioning passes totaling as much as 1 min with intermittent manual ventilation using 100% $O_2$ during the procedure. Hypoxia has been well documented during this type of clinical technique using transcutaneous $P_{O_2}$ measurements (9). Furthermore, in the four infants we studied in whom suction was not applied to the catheter, the response persisted. Broncho–carinal stimulation alone in the absence of suctioning increased systemic blood pressure and heart rate in several other studies of patients (4,5) and animals (14). In addition, if the pulmonary responses were caused by hypoxic vasoconstriction, fentanyl would not be expected to blunt them because fentanyl has been shown not to inhibit hypoxic pulmonary vasoconstriction (15,16).

Another possible cause of the pressor responses observed could be the increases in intrathoracic pressure seen with coughing and straining. The pancuronium given with the fentanyl might well prevent these increases in intrathoracic pressure. However, pulmonary artery pressure increased considerably in excess of the increases in right and left atrial pressures in our study at the same time that the cardiac index was not significantly changed. This suggests an active vasoconstrictive process in the pulmonary circulation before the fentanyl was given, as reflected in the pulmonary vascular resistance index data.

In the study by Martin et al. (11) of patients undergoing intubation, systemic arterial pressure as well as pulmonary capillary wedge pressure increased significantly when paralyzed patients were given thiopental alone, but not when fentanyl (8 $\mu$g/kg) was added to the thiopental. Because paralyzed patients were studied, changes in intrathoracic pressure due to straining were not a factor in the pressor responses seen. Although pulmonary vascular resistance was not measured in their study, the pulmonary capillary wedge pressure increased with intubation. The increase in pulmonary capillary wedge pressure may reflect changes in pulmonary venous resistance, which can be a significant component of total pulmonary vascular resistance (17,18).

The small dose of pancuronium (0.015 mg/kg) used with fentanyl in our study did not prevent spontaneous movement and thus is unlikely to have prevented, by itself, apparent pulmonary pressor response due to straining and coughing. There is little reason to suppose that systemic pressor responses would be prevented by paralysis, and, indeed, muscle relaxants alone in previous studies have not prevented increases in MAP and HR with suctioning and broncho–carinal stimulation (5,7,11).

In another study of paralyzed, lightly anesthetized patients, circulatory responses to broncho–carinal stimulation were blocked by cervical epidural blockade but not by lumbar epidural blockade (5). These circulatory responses were attributed to a sympathomimetic reflex. They occurred despite complete paralysis and were blocked only by a high sympathetic blockade. Fentanyl in sufficient doses is known to suppress sympathetic responses, and this may well be the mechanism by which fentanyl blunts the systemic pressor response to endotracheal suctioning. Although the exact role of the autonomic nervous system in regulating pulmonary vasomotor reactivity remains unclear, there is evidence for a sympathetic contribution to pulmonary vasoconstriction during stress (19,20) that might be inhibited by large doses of fentanyl.

Our present study demonstrates that stress such as brief endotracheal suctioning can provoke intense pulmonary vasoconstriction in infants even in the absence of hypoxia, as well as provoking milder systemic pressor and heart rate responses. Regardless of the genesis of the increases in pulmonary vascular resistance seen in our study, these increases represent an increased hemodynamic load to the right ventricle that may be tolerated poorly in the diseased cardiopulmonary system. Fentanyl, along with the small dose of pancuronium we used (0.015 mg/kg), was effective in preventing both the systemic and pulmonary responses to suctioning in these infants.

This study thus provides a rationale for the use of fentanyl as a primary component of the anesthetic in infants and children with either intracardiac shunting or unstable pulmonary circulations who are prone to a pulmonary hypertensive response to various sympathetic stresses, including broncho–carinal stimulation from intubation and suctioning. Although not demonstrated in our study, similar pulmonary hypertensive responses may be produced by the potent sympathomimetic surgical stresses of skin incision and sternotomy in the operating room that could be attenuated with fentanyl. Whereas other anesthetic agents can certainly blunt responses to intubation, suctioning, or other sympathomimetic stress, the ability of fentanyl to attenuate stress responses in the pulmonary circulation, to leave hypoxic pulmonary vasoconstriction intact (15,16), and to leave myocardial performance unchanged (1) should help maximize arterial oxygenation and circulatory stability in infants and neonates with ongoing or potential intracardiac shunting.

The findings of the present study suggest that use of fentanyl postoperatively in infants who have hyperreactive pulmonary circulations may be beneficial. Unstable infants with right-to-left intracardiac shunting, right ventricular failure, or decreased cardiac output secondary to pulmonary hypertension frequently require extended postoperative ventilation. In these infants, use of fentanyl in the postoperative period to prevent surges in pulmonary vascular resistance associated with suctioning, painful stimulation, and other manipulations may be beneficial until the acute period of instability is over (21). The minimum dose needed to blunt these responses was not evaluated in the present study and probably needs to be determined on an individual basis. Since these infants often require prolonged periods of postoperative mechanical ventilation in any case, profound respiratory depression with large doses of fentanyl is not usually a relevant consideration.

It must be emphasized that improper, prolonged suctioning techniques can lead to alveolar hypoxia with hypoxic pulmonary vasoconstriction, hypoxemia, bradycardia, and cardiovascular collapse. Nothing in our study suggests that fentanyl would alter this course of events. However, this study provides evidence of the effectiveness of fentanyl in reducing those potentially deleterious vasomotor responses to endotracheal stimulation in critically ill infants in the intensive care unit which can occur in the absence of prolonged suctioning procedures that cause alveolar hypoxia.

## References

1. Hickey PR, Hansen DD, Wessel DL, et al. Pulmonary and systemic hemodynamic responses to fentanyl in infants. Anesth Analg 1985;64:483–6.
2. Hickey PR, Hansen DD. Fentanyl– and sufentanil–oxygen–pancuronium anesthesia for cardiac surgery in infants. Anesth Analg 1984;63:117–24.
3. Vacanti JP, Crone RK, Murphy J, Smith SD. Treatment of congenital diaphragmatic hernia with chronic anesthesia to control pulmonary artery hypertension. Anesthesiology 1983;59:A436.
4. Fisher DM, Frewen T, Swedlow DB. Increase in intracranial pressure during suctioning-stimulation vs. rise in $P_{aCO_2}$. Anesthesiology 1982;57:416–7.
5. Dohi S, Nishikawa T, Ujike Y, Mayumi T. Circulatory responses to airway stimulation and cervical epidural blockade. Anesthesiology 1982;57:359–63.
6. Dohi S, Gold MI. Pulmonary mechanics during general anaesthesia. Br J Anaesth 1979;51:205–14.
7. White PF, Schlobohm RM, Pitts LH, Lindauer JM. A randomized study of drugs for preventing increases in intracranial pressure during endotracheal suctioning. Anesthesiology 1982;57:242–4.
8. Lowenstein E, Johnston WE, Lappas DG, et al. Catastrophic pulmonary vasoconstriction associated with protamine reversal of heparin. Anesthesiology 1983;59:470–3.
9. Zmora E, Merritt TA. Use of side-hole endotracheal tube adapter for tracheal aspiration. A controlled study. Am J Dis Child 1980;134:250–4.
10. Nicholson MJ. Cardiac arrest during therapeutic tracheal suctioning. Anesth Analg 1960;39:568–9.
11. Martin DE, Rosenberg H, Aukberg SJ, et al. Low-dose fentanyl blunts circulatory responses to tracheal intubation. Anesth Analg 1982;61:680–4.
12. Wynands JE, Wong P, Whalley DG, et al. Oxygen-fentanyl anesthesia in patients with poor left ventricular function. Anesth Analg 1983;62:476–82.
13. Sonntag H, Larsen R, Hilfiker O, et al. Myocardial blood flow and oxygen consumption during high dose fentanyl anesthesia in patients with coronary artery disease. Anesthesiology 1982;56:417–22.
14. Tomori Z, Widdicombe JG. Muscular, bronchomotor and cardiovascular reflexes elicited by mechanical stimulation of the respiratory tract. J Physiol (Lond) 1969;200:25–49.
15. Bjertnaes L, Hauge A, Kriz M. Hypoxia-induced pulmonary vasoconstriction: effects of fentanyl following different routes of administration. Acta Anaesthesiol Scand 1980;24:53–7.
16. Bjertnaes LJ. Hypoxia-induced vasoconstriction in isolated perfused lungs exposed to injectable or inhalation anaesthetics. Acta Anaesthesiol Scand 1977;21:133–7.
17. Hyman A. The direct effects of norepinephrine and of angiotensin on the pulmonary veins of intact dogs. J Pharmacol Exp Ther 1969;165:87–96.
18. Glazier JB, Murray JF. Sites of pulmonary vasomotor reactivity in the dog during alveolar hypoxia and serotonin and histamine infusion. J Clin Invest 1971;50:2550–6.
19. Fishman AP. Autonomic vasomotor tone in the pulmonary circulation. Anesthesiology 1976;45:1–2.
20. Fahmy N, Selwyn AS, Patel D, Lappas DG. Pulmonary vasomotor tone during general anesthesia and deliberate hypotension in man. Anesthesiology 1976;45:3–13.
21. Vacanti JP, Crone PK, Murphy JP, et al. The pulmonary hemodynamic response to perioperative anesthesia in the treatment of high-risk infants with congenital diaphragmatic hernia. J Pediatric Surg 1984;19:672–9.

# Anesthesia, Amnesia, and the Memory/Awareness Distinction

Eric Eich, PhD, John L. Reeves, PhD, and Ronald L. Katz, MD

EICH E, REEVES JL, KATZ RL. Anesthesia, amnesia, and the memory/awareness distinction. Anesth Analg 1985;64:1143–8.

*Several studies have shown that surgical patients cannot consciously recall or recognize events to which they had been exposed during general anesthesia. Might evidence of memory for intraoperative events be revealed through the performance of a postoperative test that does not require remembering to be deliberate or intentional? Results of the present study, involving the recognition and spelling of semantically biased homophones, suggest a negative answer to this question and imply that intraoperative events cannot be remembered postoperatively, either with or without awareness.*

Key Words: MEMORY—intraoperative.

Recent research on organic amnesia has revealed that the impairment of memory manifested by many neurologically impaired individuals is selective rather than pervasive in nature. In particular, it has been demonstrated that despite their inability to remember where they were or what they did only minutes ago, amnesic patients are able to learn new motor skills (1), acquire solutions to complex problems (2), retain classically conditioned responses (3), identify fragmented versions of recently presented pictures (4), and interpret ambiguous words in line with their experimentally biased meanings (5). What is amazing about these accomplishments is that although the patients can acquire and retain new skills and knowledge, they cannot consciously remember the circumstances under which learning took place. In other words, amnesic patients seem to have memory for recent experiences or encounters without having awareness of memory for these events (6–9).

In this experiment, we attempted to apply the distinction between memory and awareness of memory to the question of whether adequately anesthetized and apparently unconscious patients can register and retain what is said in their presence during surgery. Prior research relating to this question has focused, for the most part, on the ability of postoperative patients to recall or recognize a specific item—e.g., a spoken word, sentence, or story—as having occurred in a specific situation, namely, while the patients were experiencing the effects of general anesthesia (10–15). Memory as measured in these earlier experiments is deliberate or intentional in that the patients must be aware that they are remembering a particular past event (6,16). Because most patients appear profoundly amnesic when tested for postoperative recall or recognition of intraoperative events (10–15), it is logical to infer that, as a rule, such events are neither amenable to conscious reflection nor accessible through intentional or "aware" forms of remembering. The inference need not be drawn, however, that "patients in so-called surgical planes of anesthesia cannot hear" (15, p 89) or that anesthetized patients cannot encode and store in memory events that transpire during their surgery. The possibility remains that even though the effects of memory for intraoperative events may not—and probably cannot—be revealed in postoperative tests of retention that require remembering to be deliberate or intentional, such effects might be evident in the performance of tests that do not demand awareness of remembering.

To explore the possible dissociation between memory and awareness of memory for intraoperative events, we modeled our experiment after a recent neuropsychological study by Jacoby and Witherspoon (5). Subjects in Jacoby and Witherspoon's "spelling study" were five Korsakoff alcoholics, clinically diagnosed as amnesic, and five university students. In the first phase of the study, the subjects were asked to answer questions such as: Name a musical instrument that employs a reed. As implied by this example, the intent of the question-answering task was to encourage the

---

Preparation of this article was aided by grants to the first author from the (American) National Institute of General Medical Sciences (GM32037) and the (Canadian) Natural Sciences and Engineering Research Council (U0298).

Received from the Department of Psychology, University of British Columbia, Vancouver, British Columbia, Canada and the Department of Anesthesiology, University of California, Los Angeles, California. Accepted for publication June 25, 1985.

Address correspondence to Dr. Eich, Department of Psychology, University of British Columbia, Vancouver BC/Canada V6T 1Y7.

© 1985 by the International Anesthesia Research Society

subjects to encode homophones, such as reed, in relation to their low-frequency or less common interpretations.

In the second phase of the study, the subjects were read a list that consisted, in part, of equivalent numbers of old and new homophones—ones that either had or had not appeared in the context of biasing questions—and were asked to spell each word aloud. Jacoby and Witherspoon assumed that if the first presentation of a "biased" homophone is remembered and influences its later interpretation, more of the old than new homophones should be spelled in line with their less common interpretations. They also assumed that an influence of memory on the spelling of a word would not necessarily require the subjects to be aware that they were remembering the first presentation of that word, but that such awareness would be required in the test of old/new recognition memory that was given in the third and final phase. To the extent, then, that memory and awareness represent distinct, dissociable dimensions of human cognition, performance on a memory test (viz., recognition) that requires awareness of earlier events, and performance on a test (viz., spelling) that does not demand deliberate remembering should be independent of one another. Thus performance on one type of test should not be predictable on the basis of performance on the other type.

Evidence of such independence was revealed in two ways. First, in comparison with the students, the amnesic patients recognized fewer old homophones (25 vs 76%, with neither group of subjects generating any false alarms), but spelled more of these items in line with their less common, experimentally biased interpretations (63 vs 49%, with approximately 21% of the new homophones spelled in their low-frequency forms by both groups). Thus the disadvantage of the amnesic patients was restricted to recognition memory—an "aware" form of remembering. Second, for patients and students alike, the conditional probability of recognizing an old homophone in the third phase of the study, given that its spelling had been biased by memory in the second phase ($P(Rn/Sp)$), did not differ significantly from the unconditional probability of correct recognition ($P(Rn)$). Thus for neither type of subject was recognition memory associated with or enhanced by an effect of memory on spelling.

In summary, it appears that the prior presentation of a word has a substantial impact on its subsequent interpretation and spelling, regardless of whether or not the word is correctly classified as "old" in a later test of recognition memory. Although this dissociation of spelling and recognition performance is especially striking among the amnesics (who outperformed the students on the former test and were themselves outperformed by the students on the latter), it is demonstrated by nonamnesics as well (as evidenced by the students' statistically equivalent values of $P(Rn/Sp)$ and $P(Rn)$. Recognition and spelling thus seem to reflect fundamentally different forms or functions of memory, whether intact or organically impaired. In particular, whereas recognition of an old word requires the recognizer to be aware of its prior presentation, an influence of memory on the spelling of a word does not necessarily demand deliberate remembering (6,16).

Approached from the standpoint of anesthesia theory and practice, the idea that recognition and spelling tap different memory processes or systems raises an interesting question for research. Specifically, suppose that during surgery, an anesthetized patient listens to a series of short, descriptive phrases, each consisting of a homophone and one or two words that bias the homophone's less common interpretation (e.g., *war and* PEACE, *deep* SEA). Suppose further that several days after surgery, the patient is read a list composed chiefly of old and new homophones (i.e., ones that either had or had not been presented intraoperatively) on two successive occasions. On one occasion, the patient is simply asked to spell each list item aloud; on the other occasion, the patient is asked to state aloud which list items he or she recognizes as having been presented during surgery. Given the situation sketched above, might the patient spell significantly more old than new homophones in line with their less common interpretations, and yet fail to reliably discriminate between the two types of items in the test of recognition memory, a test, unlike that of spelling, which would require the patient to consciously reflect upon events that had occurred during a period of anesthetic unconsciousness? The main aim of the present experiment was to answer this question.

## Methods

### *Patients and Anesthetic Techniques*

Forty-eight elective surgery patients at the UCLA Health Sciences Center Hospital and Dental Clinic consented to participate in and completed all phases of the experiment. (Four patients were invited but declined to participate in the experiment. Twenty-nine patients consented to participate but did not complete the experiment, either because of failure to return for scheduled postoperative testing (18 cases) or technical difficulty in presenting or in testing the memory material (11 cases).) Of these 48 patients, 24 underwent major orthopedic surgery (e.g., Harrington rod removal or total hip replacement) and 24 underwent minor oral surgery (e.g., extraction of impacted third or fourth molars). Although both types of surgery were performed using general anesthesia, the specific anesthetic techniques involved in each type were different, as will be detailed shortly. By incorporating surgery type (orthopedic vs oral) into the design of the present experiment, we sought to increase the generality of our results.

Orthopedic and oral surgery patients averaged 31.3 and 24.4 yr of age, respectively; about 67% of the patients in both samples were women. The criteria for inclusion in either sample were age (18–50 yr); intact hearing; fluency in spoken and written English; anesthesiologist's ASA class rating of I or II; no history of cerebrovascular disease, neurological damage, or concurrent medical problems that would seriously affect surgical prognosis; no past or present drug addiction; and no chronic treatment with psychiatric medication.

For purposes of orthopedic surgery, patients received a narcotic for preanesthetic medication, either meperidine or morphine, usually combined with diazepam, hydroxyzine, or promethazine. Induction of anesthesia was with sodium thiopental, and anesthesia was maintained with nitrous oxide–oxygen plus enflurane, halothane, isoflurane, fentanyl, or meperidine. Muscle relaxants used were atracurium, pancuronium, or succinylcholine. Respiration was controlled and, when appropriate, antagonism of the neuromuscular block was accomplished with either edrophonium, neostigmine, or pyridostigmine. For purposes of oral surgery, anesthesia was produced with sodium hexobarbital and was preceded by the administration of an analgesic, an anxiolytic, and an anticholinergic agent (butorphanol, diazepam, and glycopyrrolate, respectively).

### Test Procedures and Materials

Patients were individually interviewed on two occasions: once preoperatively (about one day prior to scheduled orthopedic surgery; about 1 hr prior to scheduled oral surgery), and again postoperatively (on the average, 4.1 days after orthopedic surgery; 4.8 days after oral surgery). Both interviews were conducted either in the patients' rooms or in a secluded corner of the dental clinic.

At the outset of the preoperative interview, the patients were informed that the purpose of the experiment was to examine the effects of general anesthetics on memory for verbal material. To that end, they would be auditorily presented, either before or during surgery, with a list composed of short descriptive phrases (*laguna* BEACH, *true* BLUE, and *my fair* LADY were read as examples), and would be tested for retention of the phrases several days after surgery.

Once they had read and signed a detailed (and UCLA approved) consent form, the patients were told whether the list would be presented to them before surgery (in which case the list was presented in the manner described below) or during surgery (in which case the preoperative interview was concluded). The assignment of patients to presentation conditions (preoperative vs intraoperative) was both random and counterbalanced across surgery types.

Every patient was presented, either preoperatively or intraoperatively, with one of two equivalent lists (designated as lists A and B), each composed of 12 different descriptive phrases. Each phrase consisted of a homophone and one or two words that were intended to bias the homophone's less common interpretation (e.g., *dinner at* EIGHT, *grecian* URN). Based on normative data (17), the probability of spelling a given homophone in line with its less common interpretation (e.g., EIGHT as opposed to ATE) averaged 0.266 for list A and 0.264 for list B. Every patient was presented with his or her randomly assigned list 12 times, in a different random order of phrases each time, at a rate of 3 sec/phrase, for a total presentation time of 7.2 min. An audio cassette containing the 12 presentations of list A and a second cassette containing the 12 presentations of list B were recorded in a male voice and were alphabetically coded; throughout the course of the experiment, no one involved in interviewing or testing the patients knew the specific contents of either cassette. For purposes of preoperative presentation, the experimenter was solely responsible for fitting the patients with stereo headphones and for playing them the appropriate cassette at a comfortable listening volume of approximately 60 dB; for purposes of intraoperative presentation, the experimenter was assisted in carrying out these duties by the attending anesthesiologist. To ensure that patients assigned to the intraoperative presentation condition were adequately anesthetized while the cassette was being played, presentation of the appropriate list began when the initial surgical incision was made.

At the outset of the postoperative interview, the patients were asked to recall any experiences or dreams they might have had during surgery. Next, half of the patients were given a test of spelling followed by a test of recognition; the remaining patients completed these tests in the reverse sequence. The assignment of patients to test orders (spelling followed by recognition vs recognition followed by spelling) was random and was counterbalanced across both surgery types and presentation conditions.

For the spelling test, patients were read a list of 48 words and were asked to spell each word aloud. Of the 48 test words, 12 were old homophones (ones that had been presented to a particular patient either preoperatively or intraoperatively), 12 were new homophones (ones that had not been previously presented to that patient), and 24 were new nonhomophones (words not previously presented, intended to prevent the patient from becoming sensitized to the homophonic nature of the other items included in the test list). The 48 test words were recorded in a random order on audio tape by the same person whose voice appeared on the list-presentation cassettes, and were read to the patients at a rate of 6 sec/word. If a patient, when probed with one of the test homophones, expressed uncertainty as to which spelling to give, he or she was asked to spell the word in line with the first interpretation that came to mind.

For purposes of the recognition test, the patients were read a rerandomized tape-recorded list of the same 48 words that had been (or would be) tested for spelling. As each test word was read, the patients were asked to state aloud whether the word was "old" (one that a particular patient recognized as having been presented either preoperatively or intraoperatively) or whether it was "new" (a word that had not been presented either before or during surgery). The test of recognition, like that of spelling, was patient-paced. On completion of the last test (either recognition or spelling), the patients were thoroughly debriefed.

## Results

### *Recall*

Of the 48 patients who participated in this experiment, 42 professed to be completely amnesic for events that had taken place while they were anesthetized. Of the remaining six patients, four had a vague recollection of having dreamt during surgery, and two provided accurate retrospective reports of actual intraoperative events. One of the latter two patients was a young man who, while driving home several hours after oral surgery, suddenly remembered hearing the phrase *grecian* URN while he was asleep under anesthesia. The patient could not recall how often he had heard the phrase—it had in fact been presented to him 12 times—and he did not remember ever being awake or aware during surgery.

The only other patient who was able to recall specific intraoperative events did remember being aware of her surroundings during oral surgery. This was a young woman who claimed that she had clearly heard the list of descriptive phrases, and had been pleasantly distracted by their presentation. Nevertheless, the patient could not recall any of the phrases, and her performance on the tests of homophone recognition and spelling did not exceed chance. More interestingly, the patient also claimed that shortly after the list had been presented and the headphones had been removed, she heard someone complain of difficulty in placing an intravenous tube in her arm and someone else complain about her weight. Two independent observers confirmed to us that these complaints had indeed been made. The patient was understandably disturbed not only by what she had heard, but also by her surgeon's skeptical attitude towards her story. While the patient's story is unusual, and therefore apt to be disbelieved, it is by no means unique: anecdotal accounts of patient awareness during general anesthesia have been appearing in the literature for years (18,19), and the circumstances under which such awareness occurs has been a subject of enduring clinical concern (20,21).

### *Recognition and Spelling*

Results of the recognition test, in the form of mean proportions of old and new homophones that were classified as "old" (recognition hits and false alarms, respectively), are depicted in Figure 1 as a function of presentation condition. Inspection of these results reveals that although the patients had little difficulty discriminating between new homophones and ones that had been presented before surgery (recognition hits outnumbered false alarms by roughly a 3:1 margin), they were at a complete loss to distinguish new homophones from ones that had been presented during surgery (false alarms slightly outnumbered recognition hits). The combination of these sharply contrasting patterns produced a highly significant interaction between presentation conditions (preoperative vs intraoperative) and homophone types (old vs new) [$F(1/40) = 57.99$, $MSe = 0.05$, $P < 0.01$]. This interaction was evident in the recognition performance of both the orthopedic and the oral surgery patients ($P > 0.10$), and it emerged irrespective of whether recognition was tested before or after spelling ($P > 0.10$).

Results of the spelling test paralleled those found for recognition. As is apparent in Figure 2, the probability of spelling a homophone in line with its biased or less common interpretation was higher for old than for new homophones, but only if the old homophones had been presented in their biased forms before rather than during surgery. Analysis of the spelling data demonstrated that the interaction of presentation con-

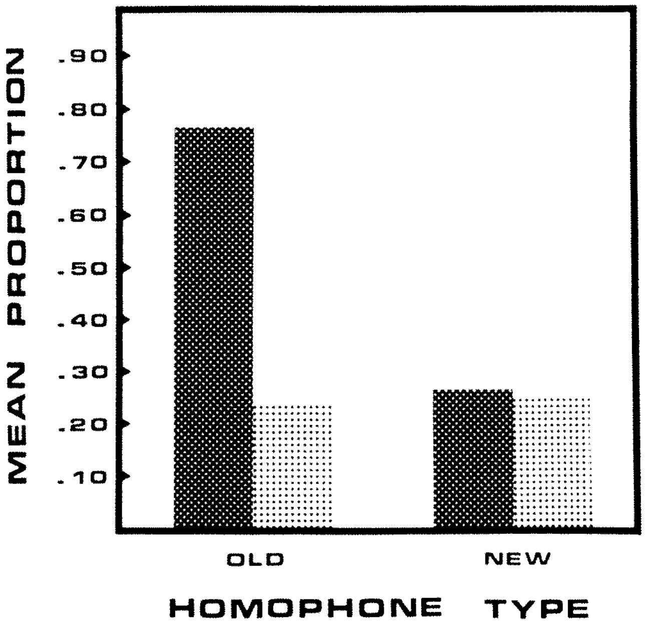


Figure 1. Mean proportions of old and new homophones that were classified as "old" in the test of recognition memory under conditions of preoperative and intraoperative presentation (black and gray bars, respectively).

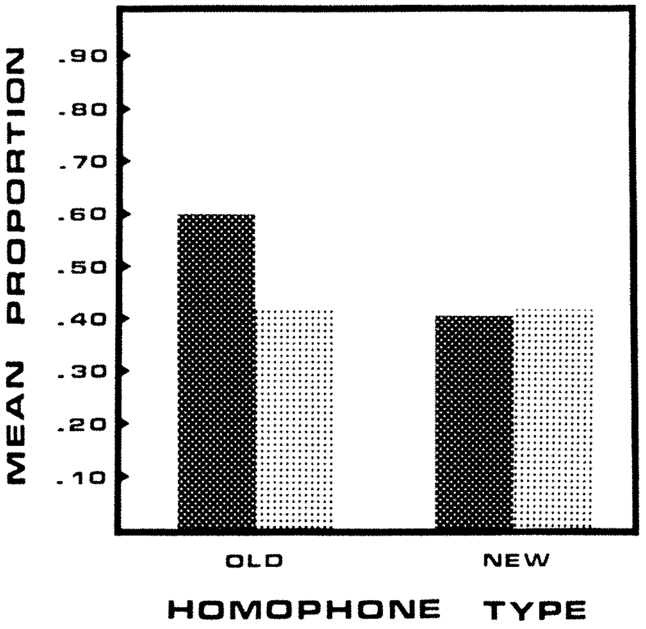


Figure 2. Mean proportions of old and new homophones that were spelled in line with their less common interpretations under conditions of preoperative and intraoperative presentation (black and gray bars, respectively).

ditions with homophone types was both reliable [$F(1/40) = 9.24$, $MSe = 0.04$, $P < 0.01$] and consistent across surgery types and test orders ($Ps > 0.10$). Viewed as a whole, our results strongly suggest that intraoperative events are neither consciously remembered nor retained in a form that is expressable through nonreflective verbal behavior. Implications of the present results for future studies of surgical memory and awareness are discussed in the next section.

## Discussion

Evidence from several studies (10–15) suggests that surgical patients cannot consciously remember events that occur in the context of anesthetic unconsciousness. On the basis of this evidence, many clinicians and researchers have assumed that sensory stimuli are neither registered nor retained in the anesthetized state. However, the available data do not rule out the possibility that intraoperative events leave lasting impressions in memory that can be revealed only through the performance of postoperative tests that do not require conscious or reflective forms of remembering. More simply stated, it is possible that postoperative patients know something about intraoperative events, but do not know that they know.

In the present study, we sought—but failed to find—evidence of a dissociation between memory and awareness of memory for intraoperative events. Participants in this study showed no sign of memory for verbal material (semantically biased homophones) to which they had been exposed repeatedly during surgery, regardless of whether their memory was tested by a test that required remembering to be deliberate or intentional (viz., recognition), or by a test that did not demand awareness of remembering (viz., spelling). Because patients who had studied the same material preoperatively provided clear evidence of retention through their performance on both the recognition and the spelling test, it cannot be argued that patients in the intraoperative presentation condition did not stand a chance of scoring highly on either test. It can be argued, however, that the chances of demonstrating effects of memory for intraoperative events might have been better had the patients been presented with information pertinent to their well being rather than with personally irrelevant items, had presentation of the information coincided with a transient or sustained lightening of the patients' anesthetic level, or had the patients performed a nonreflective test of retention that involved motor or physiologic reactions rather than verbal report (22–25). Whether there is any substance to these arguments is an important issue that remains to be settled through future experimental studies of surgical memory. At present, however, the conclusion appears compelling that intraoperative events cannot be postoperatively remembered—either with or without awareness.

Our thanks to Drs. JM Eich and LF Walts for their cogent comments on a number of clinical and conceptual issues; to Mss. K Pape and E Maslow for their outstanding technical assistance; to Drs. E Dawson, H Hargis, R Jarvis, E Johnson, J Moreland, C Pradel, G Purcell, R Smith, and other members of the UCLA medical staff for allowing us to test their patients; and most of all, to the patients themselves.

## References

1. Starr A, Phillips L. Verbal and motor memory in the amnesic syndrome. Neuropsychologia 1970;8:75–88.
2. Brooks DN, Baddeley AD. What can amnesic patients learn? Neuropsychologia 1976;14:111–22.
3. Weiskrantz L, Warrington EK. Conditioning in amnesic patients. Neuropsychologia 1979;17:187–94.
4. Warrington EK, Weiskrantz L. A study of learning and retention in amnesic patients. Neuropsychologia 1968;6:283–91.
5. Jacoby LL, Witherspoon D. Remembering with and without awareness. Can J Psychol 1982;36:300–24.
6. Jacoby LL. Knowing and remembering: some parallels in the behavior of Korsakoff patients and normals. In: Cermak LS, ed. Human memory and amnesia. Hillsdale, NJ: Lawrence Erlbaum Associates, 1982;97–122.
7. Jacoby LL, Dallas M. On the relationship between autobiographical memory and perceptual learning. J Exp Psychol:Gen 1981;110:306–40.
8. Moscovitch M. Multiple dissociations of function in amnesia. In: Cermak LS, ed. Human memory and amnesia. Hillsdale, NJ: Lawrence Erlbaum Associates, 1982:337–70.
9. Schacter DL, Tulving E. Memory, amnesia, and the episodic/semantic distinction. In: Isaacson RL, Spear NE, eds. Expression of knowledge. New York: Plenum Press, 1982.
10. Brice DD, Hetherington RR, Utting JE. A simple study of awareness and dreaming during anaesthesia. Br J Anaesth 1970;42:535–41.
11. Dubovsky SL, Trustman R. Absence of recall after general anesthesia: implications for theory and practice. Anesth Analg 1976;55:696–701.
12. Eisele V, Weinreich A, Bartle S. Perioperative awareness and recall. Anesth Analg 1976;55:513–8.
13. Loftus EF, Schooler J, Loftus GR, Glauber DT. Memory for events occurring under anesthesia. Acta Psychologica 1985;59:123–8.
14. McIntyre JWR. Awareness during general anaesthesia: preliminary observations. Can Anaesth Soc J 1966;13:495–9.
15. Terrell RK, Sweet WO, Gladfelter GH, Stephen CR. Study of recall during anesthesia. Anesth Analg 1969;48:86–90.
16. Eich E. Memory for unattended events: remembering with and without awareness. Mem Cog 1984;12:105–111.
17. Galbraith GG, Taschman CS. Homophone units: a normative and methodological investigation of the strength of component elements. J Verb Learn Verb Behav 1969;8:737–44.
18. Saucier N, Walts LF, Moreland JR. Patient awareness during nitrous oxide, oxygen, and halothane anesthesia. Anesth Analg 1983;62:239–40.
19. Sia RL. Consciousness during general anesthesia. Anesth Analg 1969;48:363–6.
20. Bogetz MS, Katz JA. Recall of surgery for major trauma. Anesthesiology 1984;61:6–9.
21. Wilson J, Turner DJ. Awareness during caesarian section under general anaesthesia. Br Med J 1969;1:280–3.
22. Cherkin A, Harroun P. Anesthesia and memory processes. Anesthesiology 1971;34:469–74.
23. Levinson BW. States of awareness during general anaesthesia. Br J Anaesth 1965;37:544–6.
24. Bennett HL, Davis HS. Nonverbal response to intraoperative conversation. Anesth Analg 1984;63:185.
25. Trustman R, Dubovsky S, Titley R. Auditory perception during general anesthesia—myth or fact? Int J Clin Exp Hypnosis 1977;25:88–105.

ANESTH ANALG
1985;64:1149–55

# Halothane Effects on Subendocardial Oxygen Supply–Demand Balance:

## Estimation from Intramyocardial Tissue Pressure and Left Ventricular Pressure

Young D. Kim, MD, David Nematzadeh, PhD, David E. Lees, MD, Pamela H. Wolf, PhD, John C. Rose, MD, Peter A. Kot, MD, and Thomas E. Macnamara, MB, ChB

KIM YD, NEMATZADEH D, LEES DE, WOLF PH, ROSE JC, KOT PA, MACNAMARA TE. Halothane effects on subendocardial oxygen supply–demand balance: estimation from intramyocardial tissue pressure and left ventricular pressure. Anesth Analg 1985;64:1149–55.

*We evaluated the effect of halothane on the balance of subendocardial oxygen supply and demand in six dogs by estimating the endocardial viability ratio (EVR) based on the pressure generated within the subendocardium (ENDO-IMP). Concurrently, the conventional EVR based on left ventricular pressure (LVP) was estimated and compared with the EVR based on ENDO-IMP. The subendocardial oxygen supply–demand ratio based on ENDO-IMP (IMP-EVR) was significantly less than EVR based on LVP (LVP-EVR) (0.87 ± 0.03 vs 1.07 ± 0.06, $P < 0.05$) during the control period. With 0.5% halothane administration, IMP-EVR improved significantly (1.04 ± 0.07, $P < 0.05$) while LVP-EVR remained unchanged (1.08 ± 0.09). No further changes in EVR (either IMP-EVR or LVP-EVR) were observed with increasing halothane concentrations up to 2%. The relationship between the two indices was weak ($r^2 = 0.44$, $P < 0.001$) but statistically significant. Because an estimate of EVR based on direct measurement of subendocardial tissue pressure (IMP-EVR) would reflect more accurately the oxygen supply–demand balance of this region than the LVP-EVR, our results suggest that the oxygen balance of the subendocardium improves with halothane administration. The use of LVP-EVR as a hemodynamic index of subendocardial oxygen balance during halothane anesthesia, therefore, is questionable.*

Key Words: ANESTHETICS, VOLATILE—halothane. HEART—myocardial oxygenation.

The subendocardial layer of the left ventricle (LV) is most vulnerable to ischemia in patients with and without coronary artery disease (1–4). The endocardial viability ratio (EVR), the ratio of the diastolic pressure–time index (DPTI) to the systolic pressure–time index (SPTI) calculated from left ventricular pressure (LVP) and aortic pressure (AP), has been proposed as a hemodynamic assessment of subendocardial oxygen balance (1–5). The validity of this ratio is based on the hypothesis that subendocardial muscle is perfused only in diastole and the subendocardial and total left ventricular oxygen needs change in the same direction. However, the confidence with which the EVR can predict subendocardial ischemia varies widely under various conditions. Some investigators have cautioned against the clinical application of EVR without full knowledge of its limitations (2,4–6).

The validity of EVR as an index of subendocardial ischemia largely depends on how closely LVP represents the stress that is actually developed in the subendocardial region (4,6,8). The interstitial fluid pressure of the myocardium is referred to as intramyocardial pressure (IMP). Several investigators employing different methods to estimate IMP have suggested that systolic IMP represents regional myocardial stresses (5–14). Thus systolic IMP closely reflects regional myocardial oxygen consumption. Likewise, diastolic IMP is a major factor regulating regional myocardial perfusion (1,4,6,9,13,15). Marzilli et al. (6) reported that the subendocardial blood supply and metabolic demand ratio calculated directly from the measurement of subendocardial IMP was substantially lower than EVR estimated from LVP. This suggests that conventional EVR reflects subendocardial

---

Received from the Departments of Anesthesia, Physiology and Biophysics, and Community and Family Medicine, Georgetown University School of Medicine, Washington, DC and the Anesthesia Section, Clinical Center, National Institutes of Health, Bethesda, Maryland. Accepted for publication June 26, 1985.

Address correspondence to Dr. Kim, Department of Anesthesia, Georgetown University School of Medicine, Washington, DC 20007.

© 1985 by the International Anesthesia Research Society

oxygen balance accurately only if changes in LVP are equal to changes in subendocardial IMP. However, it is likely that a discrepancy exists between the changes in subendocardial IMP and LVP with various interventions (4,6,8,11). In an earlier study, we showed that halothane depresses subendocardial IMP more than LVP (16). The objectives of the present study were to assess the effects of halothane on subendocardial oxygen balance by estimating the EVR directly from the IMP generated in the subendocardium (IMP-EVR), and to compare IMP-EVR with the conventional EVR based on LVP (LVP-EVR). A list of abbreviations is given in Table 1.

Table 1. List of Abbreviations Used Throughout the Text

| | |
|---|---|
| LV | Left ventricle |
| EVR | Endocardial viability ratio |
| IMP | Intramyocardial pressure |
| ENDO-IMP | Pressure generated within the subendocardium |
| DPTI | Diastolic pressure–time index |
| SPTI | Systolic pressure–time index |
| LVP | Left ventricular pressure |
| AP | Aortic pressure |
| IMP-EVR | Subendocardial oxygen supply–demand ratio based on ENDO-IMP |
| LVP-EVR | EVR based on LVP |
| PVC catheter | Polyvinylchloride catheter |

## Methods

Six healthy mongrel dogs weighing 18–30 kg were anesthetized with intravenous sodium pentobarbital (25–30 mg/kg), and the tracheae were intubated. Constant volume (tidal volume of 15 ml/kg), intermittent positive-pressure ventilation was instituted with 100% oxygen. Frequent analysis of arterial blood gases was performed. Ventilatory rate was adjusted to maintain normocarbia. Normal pH was maintained with intravenous sodium bicarbonate as needed. Body temperature was maintained at 36–37°C with a heating lamp and water blanket. A polyethylene catheter was inserted into a femoral vein, and 0.9% saline solution was administered at a rate of 5 ml·kg$^{-1}$·hr$^{-1}$ with an infusion pump. During surgical preparation, supplemental sodium pentobarbital (3–6 mg/kg) was administered intravenously whenever the dogs showed signs of awakening from anesthesia, such as eyelid reflex or slight movements. Supplemental sodium pentobarbital was not administered during the stabilization period or during halothane administration. A left thoracotomy was performed at the fourth intercostal space and the pericardium incised longitudinally from apex to base. Traction sutures were placed along the cut edges of the pericardium and carried up to the chest wall to expose the anterior wall of the LV. Care was taken to avoid excessive torsion of the heart about the great vessels. A high pressure polyvinylchloride (PVC) catheter (length 22 cm, inner diameter 0.2 cm, volume capacity 0.87 ml/30 cm) connected to a Statham P23Db transducer, was inserted into the LV cavity via the apical dimple for LVP measurements. An identical PVC catheter–Statham pressure transducer system was also positioned in the descending thoracic aorta (within 20 cm from ascending aorta) via a femoral artery for AP measurements.

Endocardial IMP (ENDO-IMP) was measured with a Mikro-Tip catheter transducer (Millar Instruments, Inc., Houston, TX). This catheter-tip transducer consists of an ultraminiature strain-gauge mounted on the tip of a 30-mm long, 16 gauge stainless steel hypodermic needle. This assembly permits easy insertion to any depth of the myocardium. The Mikro-Tip catheter transducer technique for the measurement of IMP was previously evaluated and compared with other available methods (14). The well-established advantages of this technique are 1) an ability to localize pressure measurements at various depths within the myocardial wall; 2) minimal trauma and distortion of the myocardial tissue at the site of pressure measurement because of the small volume occupied by the "sensor"; 3) a high frequency response (flat within 2% to 5 kHz) and insignificant time delay (90° at 35 kHz, about 7 μsec); and 4) the ability to simultaneously assess IMP with other hemodynamic events without disturbing LV global function (6,9,14,17).

The IMP needle was inserted perpendicular to the LV epicardial surface and passed into the inner quarter of the LV anterior free wall. The total wall thickness during systole was measured by inserting a 22-gauge spinal needle with premeasured depth marks until free blood flow appeared. The depth of the "sensor" was estimated by subtracting the length of the segment of the needle remaining outside the epicardium from the total length of the needle (up to the site of the microtransducer within the needle). Estimates of the depth and LV free wall thickness were also reevaluated by postmortem measurements, allowing for 28% thickening in vivo during systole (18). Because of the limitations of LV wall thickness measurements in our study, ENDO-IMP represented the pressure generated in the inner quarter of the LV wall.

While the excellent fidelity of the Mikro-Tip catheter transducer is well recognized, the dynamic characteristics of the PVC catheter–Statham pressure transducer system used for LVP and AP measurements were evaluated using the transient–response technique (19). The damped natural frequency was 79 Hz, the damping ratio was 0.20, and the undamped

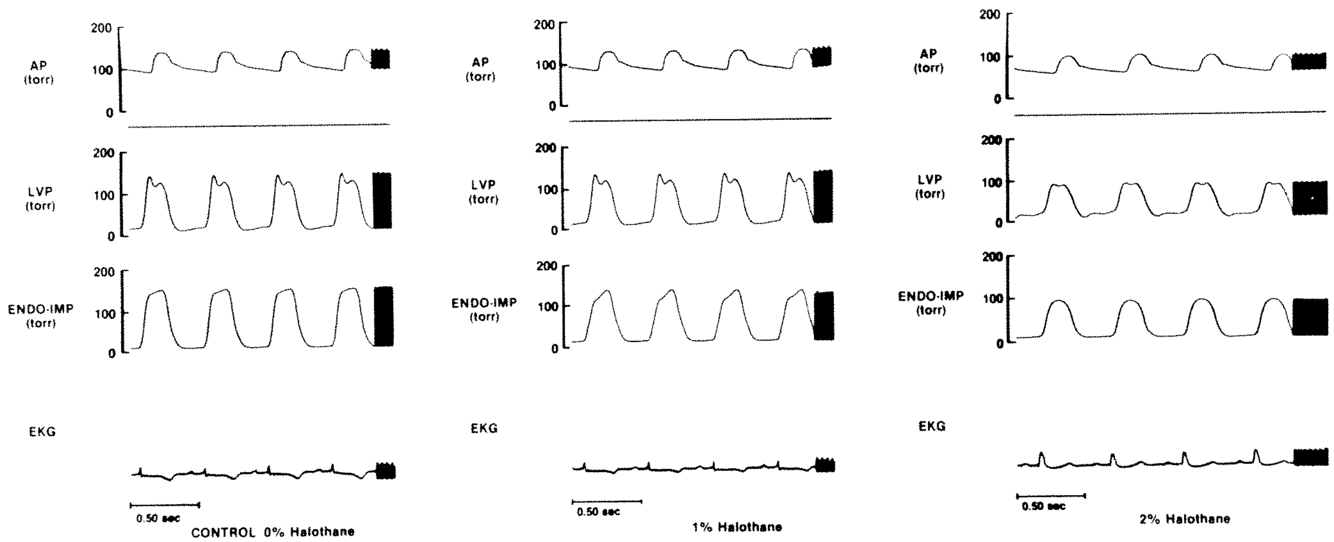


Figure 1. Tracings from one experiment showing the effects of halothane administration on pressures measured simultaneously in the descending thoracic aorta (AP), the left ventricle (LVP), and the subendocardium (ENDO-IMP) of the left ventricle. The bottom tracing represents standard limb lead II of the electrocardiogram. The halothane concentration is indicated at the lower portion of the tracing.

natural frequency was 82 Hz. From data reported by Fry (19), the amplitude response would be within 5% up to 25 Hz. In addition, measurements of LVP using this catheter-transducer system were further evaluated in vivo by comparison of simultaneous measurements using a Mikro-Tip catheter transducer. Within ranges of heart rate and blood pressure observed in our laboratory dogs during experiments (heart rate and blood pressure changes were induced by dopamine infusion, halothane anesthesia, or both), neither the amplitude nor the area contained beneath the aortic pressure curve measured with this catheter-transducer system produced an error greater than 5%.

Atmospheric pressure was considered zero for the ENDO-IMP, AP, and LVP transducers. The transducers were made equisensitive before each study. The following parameters were then recorded simultaneously on a Gould direct-writing, multichannel recorder: standard limb lead II of the electrocardiogram, AP, LVP, and ENDO-IMP. A 40-min period of stabilization was allowed to elapse before recording control values. During this period, no additional pentobarbital was administered. The halothane concentration of the inspired gas was then varied by 0.5% increments up to 2%. Halothane was delivered by a precalibrated halothane vaporizer (Mark-2). Exposure to each concentration of halothane was 20 min long (preliminary studies showed that all measured pressures (AP, LVP, and ENDO-IMP) achieved a plateau within 15 min). The end-tidal halothane concentration was not measured nor assumed to have reached a steady state. Values for LVP-EVR as well as IMP-EVR were calculated from tracings obtained at paper speeds of 200 mm/sec (4,6). The area contained beneath the LVP curve during systole (from the initiation of ventricular isometric contraction to the dicrotic notch of the AP curve) was used as SPTI. The area between the AP and LV pressure curves during diastole (from the dicrotic notch of the AP curve to the onset of ventricular contraction) was used as DPTI. DPTI was then divided by SPTI to obtain LVP-EVR. In a like manner, IMP-EVR was obtained using the ENDO-IMP curve instead of the LVP curve. Areas under the pressure curves were measured by computer-assisted planimetry with an electronic digitizer (Numonics Corp, North Wales, PA) in line with a MINC computer. At the end of each experiment, the animal was sacrificed with the heart in diastole by intravenous administration of a lethal dose of magnesium sulfate.

Analysis of variance was performed to test whether there were significant differences in the variables (pressures and EVRs). Bonferroni's multiple comparison test was then used to isolate which pairwise comparisons were significantly different. For the comparison of systolic IMP with systolic LVP during 2% halothane administration, a paired *t*-test was performed. The relationship between IMP-EVR and LVP-EVR was analyzed using linear regression analysis. A $P$ value less than 0.05 was considered statistically significant. Values were expressed as mean ± SEM.

## Results

Representative tracings obtained during one experiment are shown in Figure 1. Systolic ENDO-IMP de-

Table 2. Subendocardial Intramyocardial Pressure, Left Ventricular Pressure, Aortic Pressure, and Heart Rate with Varying Concentrations of Halothane in Six Dogs

| | Halothane (%) | | | | |
|---|---|---|---|---|---|
| | 0 (control) | 0.5 | 1.0 | 1.5 | 2.0 |
| ENDO-IMP (torr) | | | | | |
| Systole | 164 ± 6.5 | 148 ± 7.0[b] | 127 ± 7.1[b] | 118 ± 6.5[b] | 87 ± 7.9[b] |
| Diastole | 8 ± 1.9 | 9 ± 2.6 | 10 ± 1.4 | 12 ± 2.4 | 13 ± 1.2 |
| LVP (torr) | | | | | |
| Systole | 142 ± 3.2[a] | 128 ± 4.6[a,b] | 118 ± 3.8[b] | 105 ± 4.1[b] | 89 ± 5.7[b] |
| Diastole | 11 ± 1.7 | 13 ± 1.4 | 14 ± 2.2 | 15 ± 1.8 | 15 ± 1.6 |
| AP (torr) | | | | | |
| Systole | 144 ± 7.4[a] | 129 ± 5.0[a,b] | 122 ± 6.1[b] | 112 ± 6.0[b] | 93 ± 3.8[b] |
| Diastole | 110 ± 7.6 | 98 ± 6.9[b] | 91 ± 7.0[b] | 85 ± 5.8[b] | 68 ± 4.8[b] |
| HR (beats/min) | 124 ± 4.8 | 121 ± 5.4 | 108 ± 5.0 | 108 ± 4.4 | 112 ± 3.9 |

Values are expressed as mean ± SEM.
[a] $P < 0.05$ compared to systolic ENDO-IMP at each level of halothane.
[b] $P < 0.05$ compared to control values.
Abbreviations: ENDO-IMP, subendocardial intramyocardial pressure; LVP, left ventricular pressure; AP, aortic pressure; HR, heart rate.

Table 3. Estimated Endocardial Viability Ratio with Varying Concentrations of Halothane in Six Dogs

| | Halothane (%) | | | | |
|---|---|---|---|---|---|
| | 0 (control) | 0.5 | 1.0 | 1.5 | 2.0 |
| LVP-EVR | 1.07 ± 0.06 | 1.08 ± 0.09 | 1.09 ± 0.10 | 1.05 ± 0.09 | 1.03 ± 0.12 |
| IMP-EVR | 0.87 ± 0.03[a] | 1.04 ± 0.07[b] | 1.07 ± 0.11[b] | 1.03 ± 0.07[b] | 1.00 ± 0.08[b] |

Values are expressed as mean ± SEM.
[a] $P < 0.05$ LVP-EVR compared to IMP-EVR at each halothane concentration.
[b] $P < 0.05$ values compared to control.
Abbreviations: EVR, endocardial viability rate; LVP-EVR, EVR based on left ventricular pressure; IMP-EVR, EVR based on endocardial intramyocardial pressure.

creased from 150 mm Hg during the control period to 140 mm Hg with 1% halothane and further declined to 100 mm Hg with 2% halothane. Systolic LVP decreased from 140 mm Hg during control to 135 mm Hg at 1% halothane and further decreased to 100 mm Hg with 2% halothane. The effects of 2% halothane on systolic ENDO-IMP and LVP were not uniform. Systolic ENDO-IMP decreased to a greater degree than systolic LVP.

The data for all six animals are summarized in Table 2. During the control period (0% halothane), systolic ENDO-IMP was significantly greater than LVP or AP. As halothane concentration of the inspired gas was increased from 0 to 2%, systolic ENDO-IMP, LVP, and AP decreased progressively; but the decreases were not uniform. Systolic ENDO-IMP decreased (47 ± 1.4%) more than systolic LVP (36 ± 1.1%) when 2% halothane was administered ($P < 0.05$). When halothane concentration was 1% or higher, systolic ENDO-IMP approximated that of systolic LVP. Diastolic ENDO-IMP was slightly lower than LV diastolic pressure during the control period as well as during halothane administration, but the differences were not statistically significant. Heart rate remained unchanged with halothane administration.

Values for LVP-EVR under pentobarbital anesthesia alone (control, 0% halothane), were significantly higher than for IMP-EVR (Table 3). With 0.5% halothane administration, however, IMP-EVR improved significantly and approximated LVP-EVR, which remained unchanged. No further changes in IMP-EVR or LVP-EVR were observed with subsequent increases in inspiratory halothane concentration up to 2%. As shown in Figure 2, the relationship between IMP-EVR and LVP-EVR during the control period was excellent ($r^2 = 0.82$, $P < 0.01$), but the relationship was rather weak during halothane anesthesia (Fig. 3, $r^2 = 0.5$, $P < 0.001$). The relationship was further weakened ($r^2 = 0.44$, $P < 0.001$) when the values of both the control period (Fig. 2) and during halothane anesthesia (Fig. 3) were included (Fig. 4).

## Discussion

Subendocardial ischemia is one of the most common forms of myocardial injury during the perioperative period in patients both with and without coronary artery disease (1–4). A hemodynamic assessment has therefore been introduced to evaluate subendocardial

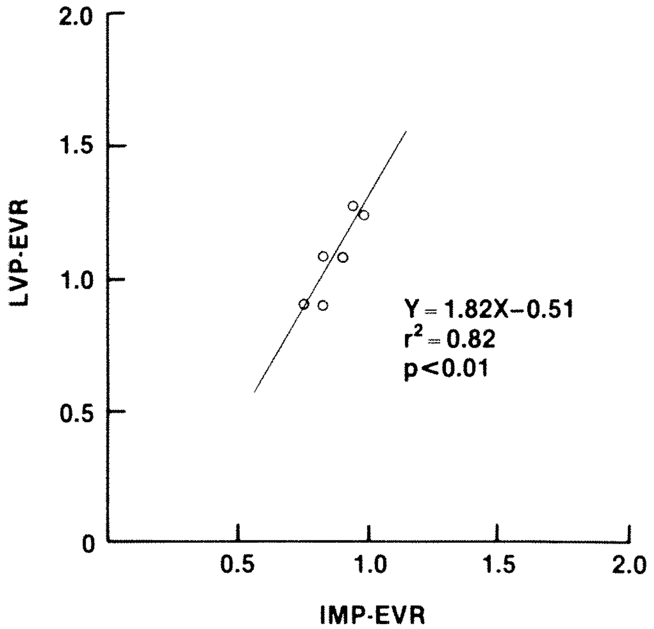


Figure 2. Relationship between endocardial viability ratio (EVR) based on left ventricular pressure (LVP-EVR) and EVR estimated directly from the subendocardial IMP (IMP-EVR) during the control period in six dogs.

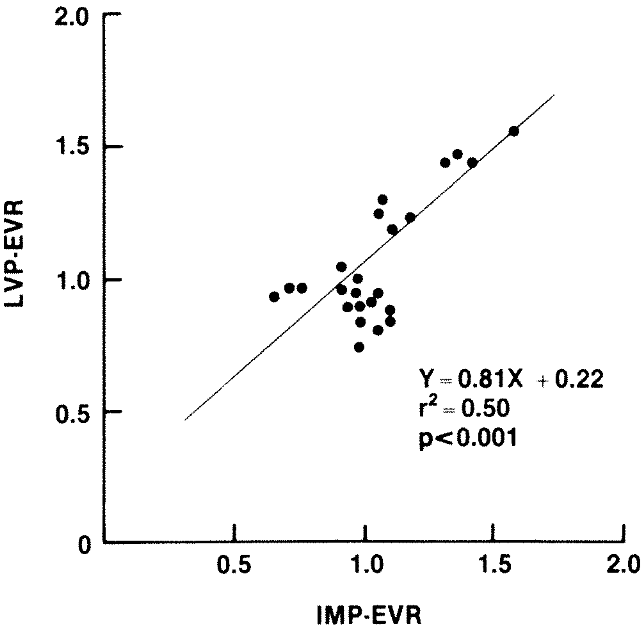


Figure 3. Relationship between endocardial viability ratio (EVR) based on left ventricular pressure (LVP-EVR) and EVR estimated directly from the subendocardial IMP (IMP-EVR) during varying concentrations of halothane in the inspired gas.

oxygen balance prior to and in critical perioperative periods (1–5). Buckberg et al. (5) suggested that relative subendocardial oxygen balance can be estimated by the ratio of DPTI to SPTI calculated from AP and LVP, respectively. This ratio, which is referred to as the endocardial viability ratio (EVR), has been utilized to predict subendocardial ischemia (1–4). Although EVR has been used to predict subendocardial oxygen balance in patients with heart disease, the application of EVR should be used with caution during the perioperative period (4–6). The present study demonstrated that inhaled halothane in pentobarbital-anesthetized dogs improved EVR based on ENDO-IMP (IMP-EVR) while the conventional EVR based on LVP (LVP-EVR) remained unchanged. Consequently, EVR as an index of subendocardial oxygen balance is severely limited during halothane anesthesia.

The major factors likely to limit the ability of EVR to estimate subendocardial oxygen balance relate to the use of SPTI as a measure of subendocardial oxygen demand and the use of DPTI for estimation of subendocardial blood flow (4,6). The use of SPTI to estimate subendocardial oxygen demand is based purely on empiric relationships. Although SPTI has been shown to change in proportion to total myocardial oxygen consumption (4,20), the relationship to subendocardial oxygen consumption is unknown.

Subendocardial IMP is the pressure generated in the subendocardial region and is a direct reflection of average regional myocardial stresses (6–15). Therefore, it is likely that subendocardial systolic IMP would be more closely related to subendocardial oxygen consumption than systolic LVP (4,6,8). Systolic subendocardial IMP has been reported to be higher, lower or the same as systolic LVP (6–8,12). This discrepancy has been attributed to the method of IMP measurement. Although no method for measuring IMP is free of all artifact, it has been generally agreed that the microtransducer method is the most reliable technique (6,9,10,14). Utilizing Mikro-Tip catheter transducers, Marzilli et al. (6) demonstrated that systolic subendocardial IMP is significantly greater than systolic LVP in intact dog hearts. Our results are consistent with their findings (14,16). SPTI based on LVP can be used as an index of subendocardial oxygen consumption only if LVP changes are proportionally and directionally the same as ENDO-IMP changes (6). However, this is not the case because sympathetic stimulation of infusion of positive inotropic agents increased systolic ENDO-IMP to a greater degree than systolic LVP, and negative inotropic agents appear to suppress systolic ENDO-IMP more than systolic LVP (7,21–23). This may explain in part why some interventions, such as $\beta$-blockers, calcium, and norepinephrine infusion cause the relationships between SPTI and myocardial oxygen consumption to be poor (24,25). In our previous study (16), halothane selectively decreased systolic ENDO-IMP more than systolic LVP. This suggests that SPTI based on LVP is a poor index of subendocardial oxygen consumption with halo-

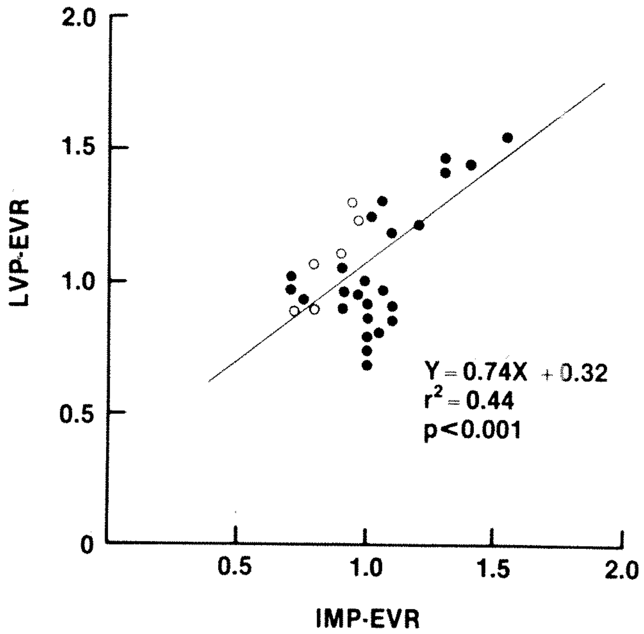


Figure 4. Relationship between endocardial viability ratio based on left ventricular pressure (LVP-EVR) and EVR estimated directly from the subendocardial IMP (IMP-EVR) during control period (○) and different concentrations of halothane in the inspired gas (●).

thane anesthesia. In the present study, similar findings were observed. Halothane administration decreased systolic ENDO-IMP more than systolic LVP, and systolic ENDO-IMP approached systolic LVP when halothane concentration was 1% or higher. These findings explain in part why LVP-EVR showed a weak relationship with IMP-EVR with halothane anesthesia.

Diastolic ENDO-IMP did not differ significantly from left ventricular end-diastolic pressure (LVEDP). Therefore DPTI based on diastolic LVP was not significantly different from the estimates based on diastolic ENDO-IMP. Our data regarding diastolic IMP are in agreement with previous reports (6,23,26). Epicardial diastolic IMP is known to be substantially higher than LVEDP and subendocardial diastolic IMP (6,9). This suggests that epicardial diastolic IMP may have a significant effect (as an extravascular compression) upon the penetrating vessels as they pass through the epicardial region. If so, estimation of endocardial blood flow from the diastolic ENDO-IMP may have to be modified by taking into consideration the epicardial diastolic IMP. This may, in part, account for the high coronary zero-flow pressure and the poor correlation between subendocardial blood flow and DPTI calculated from LVP (27,28). In our previous study, however, diastolic epicardial and endocardial IMP changed in the same direction during halothane anesthesia, supporting the validity of DPTI as an index of subendocardial oxygen supply (16). This will be particularly true when aortic diastolic pressure is high (2).

In summary, LVP-EVR was higher than IMP-EVR, thus overestimating subendocardial oxygen balance during the control period. Halothane administration improved IMP-EVR, whereas the LVP-EVR remained unchanged. Thus the relationship between these two indices was weak during halothane anesthesia. Because the IMP-EVR is more closely related to subendocardial oxygen balance than to LVP-EVR, halothane anesthesia seems to improve subendocardial oxygen balance in the intact dog heart. Further studies of low-dose halothane as a component of clinical anesthesia in patients with ischemic heart diseases are warranted.

## References

1. Hoffman JIE. Determinants and prediction of transmural myocardial perfusion. Circulation 1978;58:381–91.
2. Hoffman JIE, Buckberg GD. The myocardial supply:demand ratio. A critical review. Am J Cardiol 1978;41:327–32.
3. Phillips PA, Marty AT, Miyamoto AM. A clinical method of detecting subendocardial ischemia after cardiopulmonary bypass. J Thorac Cardiovasc Surg 1975;69:30–9.
4. Hoffman JIE, Buckberg GD. Transmural variations in myocardial perfusion. In: Yu PN, Goodman JF, eds. Progress in cardiology. Philadelphia: Lea and Febinger, 1976:37–89.
5. Buckberg GD, Fixler DE, Archie JP, Hoffman JIE. Experimental subendocardial ischemia in dogs with normal coronary arteries. Circ Res 1972;30:67–81.
6. Marzilli M, Sabbah HN, Stein PD. Supply–demand balance of subendocardial muscle: estimation from intramyocardial pressure. J Thorac Cardiovasc Surg 1980;79:803–8.
7. Armour JA, Randall WC. Canine left ventricular intramyocardial pressure. Am J Physiol 1971;220:1833–9.
8. Baird RJ, Goldbach MM, de la Rocha A. Intramyocardial pressure: the persistence of its transmural gradient in the empty heart and its relationship to myocardial oxygen consumption. J Thorac Cardiovasc Surg 1972;64:635–46.
9. Stein PD, Marzilli M, Sabbah HN, Lee T. Systolic and diastolic pressure gradients within the left ventricular wall. J Appl Physiol 1980;238:625–30.
10. Archie JP. Determinants of intramyocardial pressure. J Surg Res 1973;14:338–46.
11. Salisbury PF, Cross CE, Reiben PA. Intramyocardial pressure and strength of the left ventricular contraction. Circ Res 1962;10:608–23.
12. Kirk ES, Honig CR. An experimental and theoretical analysis of myocardial tissue pressure. Am J Physiol 1964;207:361–7.
13. Baird RJ, Adiseshiah M, Okumori M. The gradient of regional myocardial tissue pressure in the left ventricle during diastole: the relationship to regional flow distribution. J Surg Res 1976;29:11–6.
14. Nematzadeh D, Rose JC, Schryver TH, et al. Analysis of methodology for measurement of intramyocardial pressure. Basic Res Cardiol 1984;39:86–97.
15. Chiu CJ. The pathophysiology of intramyocardial pressure and blood flow distribution—a surgical perspective. J Surg Res 1974;17:278–94.

16. Nematzadeh D, Kim YD, Rose JC, et al. Effects of halothane on regional intramyocardial pressure of the canine left ventricle. Anesthesiology 1982;57:A337.
17. Sabbah HN, Marzilli M, Stein P. Ultraminiature strain gauge transducer for assessing regional intramyocardial pressure. Med Instrum 1981;15:121–4.
18. Ross JJ, Sonnenblick EH, Covell JW, et al. The architecture of the heart in systole and diastole: technique of rapid fixation and analysis of left ventricular geometry. Circ Res 1967;21:409–21.
19. Fry DL. Physiologic recording by modern instruments with particular reference to pressure recording. Physiol Rev 1960;40:753–88.
20. Sarnoff SJ, Braunwald E, Welch GH, et al. Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension–time index. Am J Physiol 1958;192:148–56.
21. D'Silva JL, Mendel D, Winterton MC. Determinants of intramyocardial pressure in the cat. Am J Physiol 1964;207:1117–22.
22. Baird RT, Manktelow RT, Shah PA, Ameli FH. Intramyocardial pressure: a study of its regional variations and its relationship to intraventricular pressure J Thorac Cardiovasc Surg 1970;50:810–23.
23. Van Der Meer JJ, Reneman RS, Schneider H, Weiberdink J. A technique for estimation of intramyocardial pressure in acute and chronic experiments. Cardiovasc Res 1970;4:132–40.
24. Jorgensen CR, Wang K, Wang Y, et al. Effect of propranolol on myocardial oxygen consumption and its hemodynamc correlates during upright exercise. Circulation 1973;48:1173–82.
25. Sonnenblick EH, Ross J Jr, Covell JN, et al. Velocity of contraction as a determinant of myocardial consumption. Am J Physiol 1965;209:919–27.
26. Kelly DT, Pitt B. Regional changes in intramyocardial pressure following myocardial ischemia. Adv Exp Med Biol 1973;39:115–30.
27. Bellamy RF. Diastolic coronary artery pressure–flow relations in the dog. Circ Res 1978;43:92–101.
28. Baller D, Duchanova HS, Zipfel J, Hellige F. Prediction of myocardial blood flow by DPTI and prediction of the adequacy of myocardial oxygen supply by the DPTI/SPTI ratio under maximal coronary dilation. Basic Res Cardiol 1979;74:378–88.

1156 ANESTH ANALG
1985;64:1156–60

# Thiopental Requirements May Be Increased in Children Reanesthetized at Least One Year after Recovery from Extensive Thermal Injury

Charles J. Coté, MD, and A. John Petkau, PhD

COTÉ CJ, PETKAU AJ. Thiopental requirements may be increased in children reanesthetized at least one year after recovery from extensive thermal injury. Anesth Analg 1985;64:1156–60.

*Clinical observations suggested that children long recovered from burn injury required larger doses of thiopental for a smooth anesthetic induction. A prospective randomized study examined children 6–16 yr old, with greater than 15% burn, and more than 1 year after injury, for loss of lid reflex (LR), corneal reflex (CR), and acceptance of the anesthesia mask (AM) 60 sec after administration of thiopental. Children were unpremedicated, received the thiopental (2.5%) through a rapidly running peripheral intravenous line, and received either 2, 3, 4, 5, 6, 7, or 8 mg/kg. LR, CR, and AM were examined at 30, 60, and 90 sec. Blood pressure and heart rate were recorded for those patients receiving 7 or 8 mg/kg thiopental. The mean age was 12.0 ± 0.5 yr, weight 43.9 ± 2.9 kg, % burn 44.7 ± 2.9, time since burn 68.4 ± 7.7 months, and time since previous thiopental 25.1 ± 6.6 months. The estimated $ED_{50}$ (95% confidence limits) for loss of LR was 4.78 (3.95–5.78) mg/kg; for loss of CR was 7.04 (4.87–10.10) mg/kg; and for AM was 6.74 (4.68–9.71) mg/kg. These doses of thiopental were significantly greater for LR and AM ($P < 0.001$) but not CR ($P = 0.15$) compared to non-thermally injured children. There were no clinically important or statistically significant decreases in blood pressure while heart rate did increase 11 beats/min ($P < 0.05$) in children who received 7 or 8 mg/kg. These data strongly suggest that thiopental requirements to ablate LR and AM in previously thermally injured children aged 6–16 yr are significantly greater than in non-thermally injured children. Logistic regression found no relationship with age, weight, % burn, time since injury, thiopental exposures, previous anesthetics, or time since last thiopental exposure.*

Key Words: ANESTHETICS, INTRAVENOUS—thiopental. COMPLICATIONS—burns.

It has been our clinical impression that children who have recovered from major burn injuries require larger doses of thiopental than non-thermally injured children to achieve a satisfactory induction to general anesthesia. In order to document this observation, we undertook a randomized prospective study, examining several commonly used indicators for induction of anesthesia after thiopental administration: the loss of lid reflex (LR), the loss of corneal reflex (CR), and acceptance of the anesthesia mask (AM).

## Methods

This study was approved by the Subcommittee on Human Studies at the Massachusetts General Hospital and the Shriners Burns Institute. Thirty-six patients between the ages of 6 and 16 yr who did not want a mask induction or premedication were studied. They had previously suffered a greater than 15% body surface burn, and desired an intravenous induction to anesthesia. All children studied were scheduled for plastic reconstructive surgery at least 12 months after acute burn injury; none gave a history of taking chronic medications. All were ASA status I–II patients who had intact eyelashes. Thiopental (2.5%) was administered through a rapidly running intravenous line at a dose of 2, 3, 4, 5, 6, 7, or 8 mg/kg. The induction doses were chosen by assignment of random number. When it became clear that there was not a clean upper limit for thiopental requirements, additional children were assigned to receive the higher

---

Presented in part at the Annual Meeting of the American Society of Anesthesiologists, October 1981.

Received from the Anesthesia Services of the Massachusetts General Hospital and Shriners Burns Institute, and the Department of Anesthesia, Harvard Medical School, Boston, Massachusetts. Accepted for publication June 14, 1985.

Address correspondence to Dr. Coté, Department of Anesthesia, Massachusetts General Hospital, Boston, MA 02114.

Current address for Dr. Petkau is the Department of Statistics, University of British Columbia, Vancouver, BC, Canada V6T 1W5.

© 1985 by the International Anesthesia Research Society

Table 1. Estimated $ED_{50}$ (95% Confidence Limits) for Loss of Each Response in Burned vs Unburned Children (1)

| | $ED_{50}$ (mg/kg) | |
|---|---|---|
| Reflex | Burned ($n$ = 36) | Unburned ($n$ = 54) |
| Lid | 4.78 (3.95 – 5.78) | 2.95 (2.40 – 3.61)[a] |
| Corneal | 7.04 (4.87 – 10.10) | 4.90 (3.47 – 6.92)[b] |
| Accept mask | 6.74 (4.68 – 9.71) | 2.68 (1.98 – 3.62)[a] |

[a] $P < 0.001$; [b] $P = 0.15$, not significant.

doses thus accounting for the slight imbalance for each dose administered. Patients were divided into seven groups based on the dose received. Each patient was examined at 30, 60, and 90 sec after thiopental administration for the presence or absence of the LR, CR, and AM. The lid reflex was induced by gently brushing both lashes with a fingertip. The corneal reflex was induced by softly touching the cornea with a sterile gauze sponge. Mask acceptance was assessed by placing the mask gently on the face, moving the chin to the "sniffing" position, and beginning assisted ventilation. Positive LR and CR responses were recorded when blinking followed the stimulus. Rejection of the anesthesia mask as assessed in our previous study of unburned children, consisted of turning the head or pushing the mask with his or her hand and not allowing assisted ventilation (1). No medications other than oxygen were administered during the study period. Additional thiopental was administered at 90 sec if clinically indicated as judged by movement of the patient, phonation, or coughing. Induction was considered satisfactory if there was a smooth transition between the initial thiopental and the start of general anesthesia.

All observations were confirmed by an independent physician (resident or staff) not involved in the study. These results were compared to the data from 54 non-thermally injured children previously studied in a similar fashion (1). The period 60 sec after thiopental administration was found to be the optimal time of examination in the previous study, as it was in the present study; this also allowed for comparison between this and the previous study. Other data recorded were age, weight, time since burn injury, the number of previous known anesthetics, the number of previous known exposures to thiopental, and the time since last exposure to thiopental.

Logistic regression analysis established the $ED_{50}$ values and was also employed to interpret available covariate factors for both studies. Tests of equality of $ED_{50}$ values provided an overall comparison of the responses of thermally injured and non-thermally injured patients. ANOVA was used to compare age data between dose groups for both the thermally injured and non-thermally injured patients. Two-sample tests compared age data and evaluated blood pressure and heart rate changes. All results are expressed as mean ± 1 SEM unless otherwise indicated. Results were considered significant when $P < 0.05$.

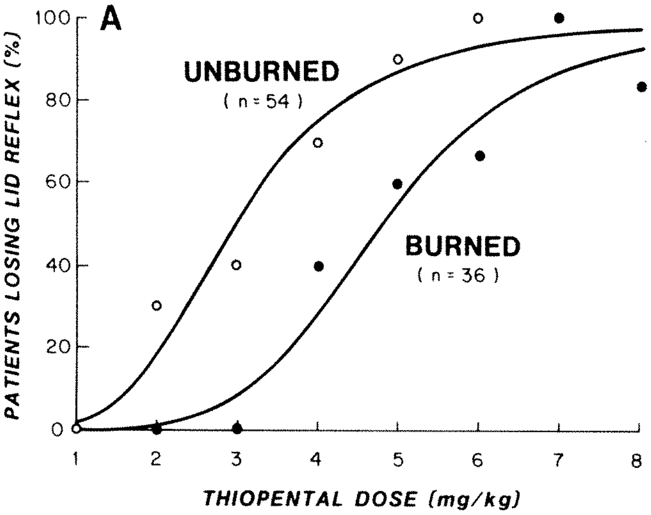


Figure 1. Loss of lid reflex and thiopental dosage in burned (solid circle) and unburned children (open circle). The difference between groups was significant ($P = 0.001$). The non-thermally injured group was studied at lower doses of thiopental because their clinical response was greater.

## Results

The estimated $ED_{50}$ values for loss of LR, CR, and AM are presented in Table 1. The $ED_{50}$ values for LR and AM were significantly greater in thermally injured than in non-thermally injured children ($P < 0.001$). Although the estimated $ED_{50}$ for CR was also greater in thermally injured than in non-thermally injured children, this difference was not significant ($P = 0.15$).

Figures 1–3 compare the dose–response relationships between thermally injured ($n = 36$) and non-thermally injured children ($n = 54$). As is apparent from the figures, there was considerable variability in AM response for non-thermally injured and CR response for thermally injured patients, which in part accounts for the lack of statistical difference in the $ED_{50}$ for CR response in the thermally injured and non-thermally injured children (Table 2). The data for age, weight, % burn, time elapsed since burn injury, the number of previous anesthetics and thiopental exposures, and the time since last exposure to thiopental are presented in Table 3. Logistic regression for the above variables found none to be explanatory in the dose–response relationship. There was no sta-

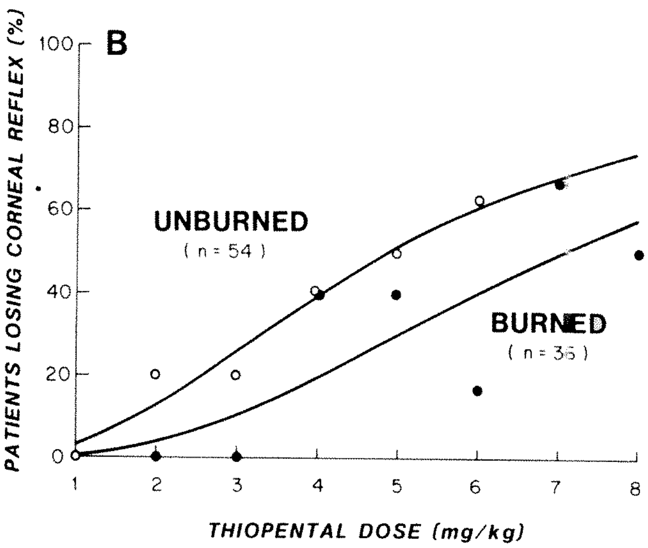


Figure 2. Loss of corneal reflex and thiopental dosage in burned (solid circle) and unburned patients (open circle). Considerable variability was observed in the thermally injured children. The non-thermally injured group was studied at lower doses of thiopental because their clinical response was greater.

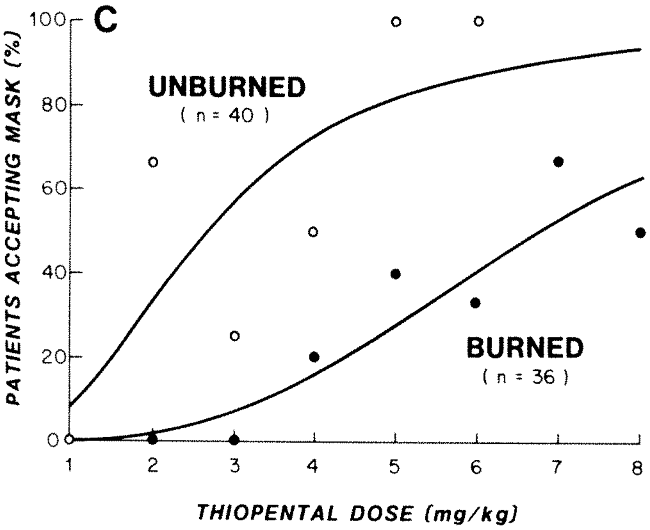


Figure 3. Acceptance of the anesthesia mask and thiopental dose in burned and unburned patients. Data from both the current study and our previous study of non-thermally injured children includes only patients who refused to accept the anesthesia mask preoperatively. Considerable variability was observed in the non-thermally injured group. The difference between groups was significant ($P = 0.001$). The non-thermally injured group was studied at lower doses of thiopental because their clinical response was greater.

tistical difference in age between dose groups for either the thermally injured or the non-thermally injured patients nor in the overall comparison of the thermally injured to non-thermally injured patients.

When examining individual reflexes as indicators of satisfactory anesthetic induction it was obvious that when LR and CR were present, all 16 patients rejected the anesthesia mask. However, of the 12 patients who lost both LR and CR after thiopental, six accepted and six rejected the mask. The remaining eight patients had variable responses. Twenty of the 24 patients who did not accept the anesthesia mask required additional thiopental to stop patient movement such as turning the head, reaching for the mask, or twisting the body.

The response of blood pressure and heart rate was recorded only for groups treated with 7 and 8 mg/kg thiopental ($n = 12$ patients). A 2-sample test found no significant change ($P = 0.20$) in systolic blood pressure at 60 sec (120.0 ± 5.4) compared to baseline (122.7 ± 6.5). There was a significant change in heart rate from 99.8 ± 4.8 beats/min at baseline to 110.9 ± 4.4 at 60 sec ($P < 0.05$). No clinically important decreases in blood pressure (>20% of baseline) were observed in any patient despite the large doses administered.

## Discussion

This study strongly suggests that the thiopental requirements ($ED_{50}$) for the ablation of the LR and acceptance of the anesthesia mask in previously thermally injured children are significantly higher compared to a similar group of non-thermally injured children ($P < 0.001$). The first 20 thermally injured children were studied concurrently with the non-thermally injured children; however, it took 15 months to collect 16 more children who did not want a premedication and did want an intravenous induction to anesthesia. Therefore, strict statistical comparison between the two groups (thermally injured and non-thermally injured children) is not sound because both studies were not carried out simultaneously. The apparent altered response of the thermally injured children was not correlated with age, weight, % burn, number of previous thiopental exposures, time since injury, or time since last exposure to thiopental when these additional explanatory variables were considered individually. Although the mean dose for the ablation of the CR was higher in the thermally injured patients, we could not demonstrate a statistical difference, primarily because of the variable response (and small sample size) in the thermally injured group (Table 2). We cannot completely rule out that these apparent increased thiopental requirements might be related to prior anesthetic experience, because 22 of the 54 non-thermally injured children to which the thermally injured children were compared were anesthetized for the first time, thus making a strict comparison difficult. On the other hand to perfectly match

Table 2. Mean Age and % of Burned Patients who Lost their Reflexes at 60 sec after Injection of Thiopental

| Thiopental (mg/kg) | Mean age (yr) | n | Lid reflex | Corneal reflex | Accept mask |
|---|---|---|---|---|---|
| 2 | 12.0 | 4 | 0 | 0 | 0 |
| 3 | 11.3 | 4 | 0 | 0 | 0 |
| 4 | 12.4 | 5 | 40 | 40 | 20 |
| 5 | 10.4 | 5 | 60 | 40 | 40 |
| 6 | 12.5 | 6 | 67 | 17 | 33 |
| 7 | 11.5 | 6 | 100 | 67 | 67 |
| 8 | 13.0 | 6 | 83 | 50 | 50 |

Table 3. Vital Statistics of the Population Studied

| | *n* | Mean ± SEM | Range |
|---|---|---|---|
| Age (yr) | 36 | 12.0 ± 0.5 | 6–15 |
| Weight (kg) | 36 | 43.9 ± 2.9 | 18–81 |
| % Burn | 36 | 44.7 ± 2.9 | 15–80 |
| Time since burn (months) | 36 | 68.4 ± 7.7 | 12–144 |
| Previous thiopental exposures | 32 | 5.8 ± 1.1 | 0–13 |
| Previous anesthetics | 34 | 11.7 ± 1.05 | 3–25 |
| Time since last thiopental (months) | 28 | 25.1 ± 6.6 | 3–144 |

patients for age, anesthetic experience, and induction preference would take years to accomplish. Thus we are left with a less than ideal control population.

The pharmacologic responses to medications administered to acutely burned patients may be altered by many factors, e.g., there is an increase in glomerular filtration rate and volume of distribution, there are alterations in protein binding, cardiac output is increased, there is possible interaction with other medications, or altered hepatic metabolism (2–5). Studies in acutely burned adults and children have found significant increases in the requirements of nondepolarizing neuromuscular blocking agents compared to unburned patients in order to achieve the same degree of neuromuscular blockade (5,6). This increased requirement is partly explained by increased protein binding and may be related to "changes at the target tissue" (7). The present study demonstrates a change in the clinical response to thiopental that apparently persists for years after recovery from acute injury.

The cause for this apparent altered patient response is unclear. The time lapse since thermal injury (mean 68 months) makes the above-described factors such as hypermetabolism, altered cardiac output, increased glomerular filtration rate, altered protein binding, or volume of distribution unlikely. The lack of a chronic medication history in these children probably rules out exogenous drug interaction. Acute tolerance to thiopental is well documented; however, in this study there was no correlation with time since last exposure or number of thiopental exposures (8). Since these children were unpremedicated it is possible that elevated levels of anxiety and the compensatory catecholamine response associated with this may have contributed to the resistance to thiopental induction. However all of these children were experienced patients and requested an intravenous induction (9). The thermally injured children in this study were slightly older (mean 12.0 yr) than the group of non-thermally injured children studied previously (mean 10.9 yr); however, detailed statistical analysis found no statistically significant differences between groups. Further, age was not found to be explanatory in the dose–response relationship for either the thermally injured or the non-thermally injured patients. This suggests that some other unknown factor has an influence on the observed responses.

The observation that despite the loss of both CR and LR, 50% of thermally injured children required more thiopental to achieve a satisfactory induction is consistent with our previous study of non-thermally injured children (1).

Concerns regarding adverse cardiovascular events after a large bolus of thiopental were not borne out. We limited our cardiovascular observations to the two highest doses of thiopental because we had no prior experience administering such large doses as a bolus. Our experience with the 12 patients in the current study who received a bolus of 7–8 mg/kg thiopental revealed none to have clinically important changes in systolic blood pressure after thiopental. The heart rate did however increase a mean of 11 beats/min; this probably represents a reflex response to venodilatation (10).

In summary, thermally injured children between the ages of 6 and 16 who have recovered from their acute injury require about 62% more thiopental than non-thermally injured children to ablate the lid reflex and 151% more thiopental to accept an anesthesia mask and begin assisted ventilation. This may be an important consideration for those children who require a rapid smooth anesthetic induction, especially under circumstances such as a full stomach, gastroesophageal reflux, or hiatus hernia. If such patients are normovolemic, then 7 to 8 mg/kg thiopental would seem to be a reasonable induction dose to assure a well-sedated child during laryngoscopy and intubation.

---

We thank Drs. J.F. Ryan and R.J. Kitz for their careful review, as well as Drs. L. Liu, N. Goudsouzian, S. Firestone, D. Dedrick, S. Szyfelbein, C. Rosow and the anesthesia residents for their assistance with this study.

## References

1. Coté CJ, Goudsouzian NG, Liu LMP, Dedrick DF, Rosow CE. The dose response of intravenous thiopental for the induction of general anesthesia in unpremedicated children. Anesthesiology 1981;55:703–5.
2. Loirat P, Rohan J, Baillet A, et al. Increased glomerular filtration rate in patients with major burns and its effect on the pharmacokinetics of tobramycin. N Engl J Med 1978;299:915–9.
3. Ciaccio EI, Fruncillo RJ. Urinary excretion of D-glucaric acid by severely burned patients. Clin Pharmacol Ther 1979;25:340–4.
4. Wilmore DW, Aulick LH, Mason AD, et al. Influence of burn wound on local and systemic responses to injury. Ann Surg 1979;186:444–58.
5. Martyn JAJ, Szyfelbein SK, Ali HH, et al. Increased *d*-tubocurarine requirement following major thermal injury. Anesthesiology 1980;52:352–5.
6. Martyn JAJ, Goudsouzian NG, Matteo RS, et al. Metocurine requirements in burned paediatric patients; the relation of plasma concentration to neuromuscular blockade. Br J Anaesth 1983;55:263–8.
7. Leibel WS, Martyn JAJ, Szyfelbein SK, et al. Elevated plasma binding cannot account for the burn related *d*-tubocurarine hypersensitivity. Anesthesiology 1982;54:378–82.
8. Toner W, Howard PG, McGowan WAW, Dundee JW. Another look at acute tolerance to thiopentone. Br J Anaesth 1980;52:1005–8.
9. Johnston RR, Way WL, Miller RD. Alterations of anesthetic requirement by amphetamine. Anesthesiology 1972;36:357–63.
10. Conway CM, Ellis DB. The haemodynamic effects of short-acting barbiturates. Br J Anaesth 1969;41:534–42.

# Epidural Ketamine for Control of Postoperative Pain

Jose-Adolfo Islas, MD, Jorge Astorga, MD, Miguel Laredo, MD

ISLAS JA, ASTORGA J, LAREDO M. Epidural ketamine for control of postoperative pain. Anesth Analg 1985;64:1161–62.

*The study was undertaken to evaluate the postoperative pain control ability of ketamine injected into the epidural space. We conclude that it produces potent postoperative analgesia without major respiratory depression or other side effects.*

Key Words: ANESTHETIC TECHNIQUES, EPIDURAL—ketamine. PAIN—postoperative. ANESTHETICS, INTRAVENOUS—ketamine.

Ketamine hydrochloride is a potent analgesic and an anesthetic (1,2). Other analgesics, like opioids, have been shown to effectively relieve postoperative pain when injected into the epidural space (3,4). Ketamine injected into the epidural space has not been evaluated for postoperative pain control, and therefore the present study was undertaken.

## Methods

Fifty patients scheduled for elective operations in lower abdomen, perineum, or lower extremities were studied. For all patients, written consent was obtained preoperatively, and a detailed neurologic examination was carried out. Operative anesthesia with lidocaine or bupivacaine was provided, using a catheter inserted at the L3–4 interspace into the epidural space.

In the recovery room, after operative anesthesia had worn off, patients were asked to classify pain as mild, moderate, or severe. Baseline levels of pain intensity, blood pressure, respiratory rate, and sensory and motor function below T10 were recorded. Ketamine hydrochloride, 4 mg, diluted in 10 ml 5% dextrose in water was then injected via the epidural catheter. All patients received only one injection each of ketamine. Patients were observed until either pain returned or 6 hr had elapsed. All measurements made before injection of ketamine were repeated 5, 10, 15, and 30 min, and every half-hour thereafter until pain returned or until the study was discontinued after 6 hr. Within 24–72 hr of the injection, neurologic examination was repeated.

## Results

Patient population, the types of operations, and the severity of postoperative pain are summarized in Tables 1, 2, and 3. Pain relief, defined as the absence of pain or the presence of only mild pain, was obtained in all patients treated with epidural ketamine. The onset of analgesia was detectable within 5–10 min and it was complete within 15–30 min. The mean duration of pain relief averaged 4.06 ± 1.34 hr SD (range 1.5–5.5 hr). The duration of pain relief varied from 1.5 hr in three cases to over 5 hr in 42% of the cases. In 60% of the cases pain relief exceeded 4 hr.

There was no evidence of respiratory depression, urinary retention, or other side effects in any patient, and there were no postoperative neurologic sequelae. The epidural injection of ketamine produced no discomfort.

## Discussion

These results demonstrate that epidural ketamine provides postoperative analgesia. The cardiovascular effects usually associated with the use of ketamine (5) were not observed, nor was there evidence of sensory, motor or sympathetic block. The absence of neurologic changes apart from pain relief suggest that selective epidural analgesia was achieved.

Ketamine has been administered intrathecally to baboons without side effects (6) and epidurally to humans suffering from intractable pain (7). In view of the small amounts of ketamine used epidurally and intrathecally, it is unlikely that the effects are due to systemic absorption of the drug. Also, although pla-

---

Received from the Department of Anesthesiology, Instituto Nacional de la Nutrición, Mexico City, Mexico. Accepted for publication June 7, 1985.

Address correspondence to Dr. Islas, Instituto Nacional de la Nutrición, Vasco de Quiroga No. 15, Delegación Tlalpan, México D.F. 14000, México.

© 1985 by the International Anesthesia Research Society

Table 1. Patient Population and Initial Postoperative Pain Intensity

| Sex ($n$) | Age[a] (yr) | Initial pain intensity Mild | Moderate | Severe |
|---|---|---|---|---|
| Male (27) | 53.4 ± 18.1 | 11 | 5 | 11 |
| Female (23) | 43.9 ± 10.7 | 8 | 3 | 12 |

[a] Mean ± SD.

Table 2. Types of Operations

| Operation | Number of patients |
|---|---|
| Inguinal herniorrhaphy | 14 |
| Supracondylar amputation | 9 |
| Colpoperinorrhapy | 7 |
| Transurethral prostatectomy | 7 |
| Hemorrhoidectomy | 6 |
| Vaginal hysterectomy | 4 |
| Cystolithotomy | 3 |
| Total | 50 |

Table 3. Mean (± SD) Pain Scores[a] before and after Epidural Ketamine

| Before ketamine | After epidural ketamine 15 min | 30 min | 1 hr | 5.5 hr |
|---|---|---|---|---|
| 2.5 ± 0.5 | 0.8 ± 0.9 | 0.4 ± 0.5 | 0.13 ± 0.35 | 0.13 ± 0.35 |

[a] 1, mild pain; 2, moderate pain; 3, severe pain.

cebos relieve pain about one-third of the time (8,9), because ketamine produced pain relief in all our patients it is unlikely that the pain relief associated with epidurally administered ketamine represents a placebo response. More likely, ketamine, which has been reported as able to produce lamina-specific inhibition of dorsal horn unit activity (10) and to interact as an agonist with opiate receptors (11,12), produced segmental analgesia by diffusing across the dura and acting directly on the cord in the same way that opioids do (13), despite the findings by Fratta et al. (14) that ketamine fails to interact with opiate receptors and is not antagonized by naloxone.

We conclude that epidural injection of ketamine produces potent postoperative analgesia without major respiratory depression or other side effects. The present results indicate the need for further studies to compare the efficacy and safety of epidural ketamine with the response to epidural opioids for the relief of postoperative pain.

## References

1. Slogoff S, Allen GW, Wessels JV, Chessey DH. Clinical experience with subanesthetic ketamine. Anesth Analg 1974;53:354–8.
2. White PF, Way WL, Trevor AJ. Ketamine: its pharmacology and therapeutic uses. Anesthesiology 1982;56:119–36.
3. Bromage PR, Camporesi E, Chestnut D. Epidural narcotics for postoperative analgesia. Anesth Analg 1980;59:473–80.
4. Brownridge PR. Epidural and intrathecal opiates for postoperative pain relief. Anaesthesia 1983;38:74–5.
5. Waxman K, Shoemaker WC, Lippmann M. Cardiovascular effects of anesthetic induction with ketamine. Anesth Analg 1980;59:355–8.
6. Brock-Utne JG, Kallichurum S, Mankowitz E, Maharaj RJ, Downing JW. Intrathecal ketamine with preservative. Histological effects on spinal nerve roots of baboons. S Afr Med J 1982;61:440–1.
7. Mankowitz E, Brock-Utne JG, Cosnett JE, Green-Thompson R. Epidural ketamine: a preliminary report. S Afr Med J 1982;61:441–2.
8. Collins JK, Juras EP, Van Houten RJ, et al. Intrathecal cold saline solution: a new approach to pain. Anesth Analg 1969;48:816–22.
9. Savitz MH, Malis LI. Intrathecal injection of isotonic iced saline for intractable pain. Mount Sin J Med 1972;39:134–45.
10. Kitahata LM, Taub A, Kosaka Y. Lamina-specific suppression of dorsal-horn unit activity by ketamine hydrochloride. Anesthesiology 1973;38:4–11.
11. Smith DJ, Westfall DP, Adams JD, et al. Ketamine interacts with opiate receptors as an agonist. Anesthesiology 1980;53:S5.
12. Kinck AD, Ngai SH. Opiate receptor mediation of ketamine analgesia. Anesthesiology 1982;56:291–7.
13. Yaksh TL. Spinal opiate analgesia: characteristics and principles of action. Pain 1981;11:293–346.
14. Fratta W, Casu M, Balesterieri A, et al. Failure of ketamine to interact with opiate receptors. Eur J Pharmacol 1980;61:389–91.

# Central Serotonin Depletion:
## Effect on Blood Pressure during Anesthesia

John S. Althaus, MS, Judy J. Beckman, BS, and Edward D. Miller Jr, MD

ALTHAUS JS, BECKMAN JJ, MILLER ED JR. Central serotonin depletion: effect on blood pressure during anesthesia. Anesth Analg 1985;64:1163–70.

*Serotonin (5-HT) in the central nervous system has been implicated in blood pressure control in both normotensive and hypertensive states. Parachlorophenylalanine (PCPA) depletes 5-HT in the central nervous system. Normotensive Wistar rats, Wistar rats made hypertensive by renal artery clipping (RHR), and spontaneously hypertensive rats (SHR) were depleted of central serotonin by the administration of PCPA. Mean arterial blood pressure (MAP), heart rate (HR), and plasma norepinephrine (NE) levels were measured in rats both before and after they were administered anesthesia with enflurane. Blood pressure was further decreased by the administration of saralasin, a competitive inhibitor of angiotensin II. Principal results are as follows. Central 5-HT was depleted by 70% or more with PCPA. In general, brain catecholamines were not altered by this treatment. No consistent pattern of change in MAP, HR, or plasma NE was observed for Wistar rats, RHR, or SHR during an awake control period in rats treated with PCPA compared with rats treated with vehicle. However, during enflurane anesthesia or enflurane anesthesia with saralasin, MAP, HR, and plasma NE were significantly greater in Wistar rats and RHR treated with PCPA compared to similar groups treated with vehicle. This was not observed in SHR: MAP, HR, and plasma NE were similar to vehicle-treated SHR. Nonsignificant changes in plasma epinephrine, plasma renin activity, or arterial blood gas tensions could not explain the differences seen in Wistar rats, RHR, or SHR. Central serotonin plays an important role in cardiovascular control during anesthesia with enflurane in Wistar rats but does not appear to play a dominant role in SHR.*

Key Words: BRAIN—serotonin, catecholamines. SYMPATHETIC NERVOUS SYSTEM—catecholamines. POLYPEPTIDES—renin, angiotensin.

Blood pressure during anesthesia is influenced by a variety of factors. Anesthetic agents themselves are known to influence vascular smooth muscle (1), cardiac contractility (2), baroreceptor function (3), and sympathetic nervous system activity (4). Coincident with the effects of anesthetic agents on end organ function, hormonal and neurotransmitter activity is also altered (5–7). Previous reports from our laboratory have examined the role of the renin–angiotensin system in blood pressure support during anesthesia (8,9). We have used a variety of experimental techniques to better define this role. Subsequently, we have reported experiments defining the role of both the central and the peripheral sympathetic nervous systems in blood pressure control (10,11).

We recognize that a variety of other hormones and neurotransmitters may also be important in blood pressure control during anesthesia. Recently, the central monoaminergic neuronal system has been proposed as an important factor in blood pressure control in both normotensive and hypertensive animals (12). There are both ascending and descending serotonergic (5-HT) nerves in the brain that may have different effects on blood pressure (13). Coote and MacLeod (14) have proposed a sympatho-inhibitory function for descending bulbospinal 5-HT nerves, and Wolf et al. (15) have demonstrated activation of ascending 5-HT nerves innervating the anterior hypothalamus that has produced pressor responses.

To determine whether blood pressure alterations produced by anesthetic agents were mediated in part by the serotonergic nervous system, central 5-HT was depleted in normotensive rats and in rats with either renovascular hypertension (RHR) or genetic spontaneous hypertension (SHR). 5-HT depletion was produced by the peripheral administration of parachlorophenylalanine (PCPA), a drug known to deplete central serotonin stores by irreversibly inhibiting tryptophan hydroxylase (16). Animals so depleted were then anesthetized with enflurane, and cardiovascular

---

Supported in part by National Institutes of Health grant RO-1-GM 24313-07.

Received from the Department of Anesthesiology, University of Virginia, Charlottesville, Virginia. Accepted for publication June 11, 1985.

Address correspondence to Dr. Miller, Department of Anesthesiology, Box 238, University of Virginia Medical Center, Charlottesville, VA 22908.

© 1985 by the International Anesthesia Research Society

and hormonal responses were measured. The renin–angiotensin system was then inhibited through the use of saralasin, a specific inhibitor of angiotensin II, in order to decrease blood pressure further. Through these experiments we sought to determine the role of 5-HT in blood pressure control during enflurane anesthesia.

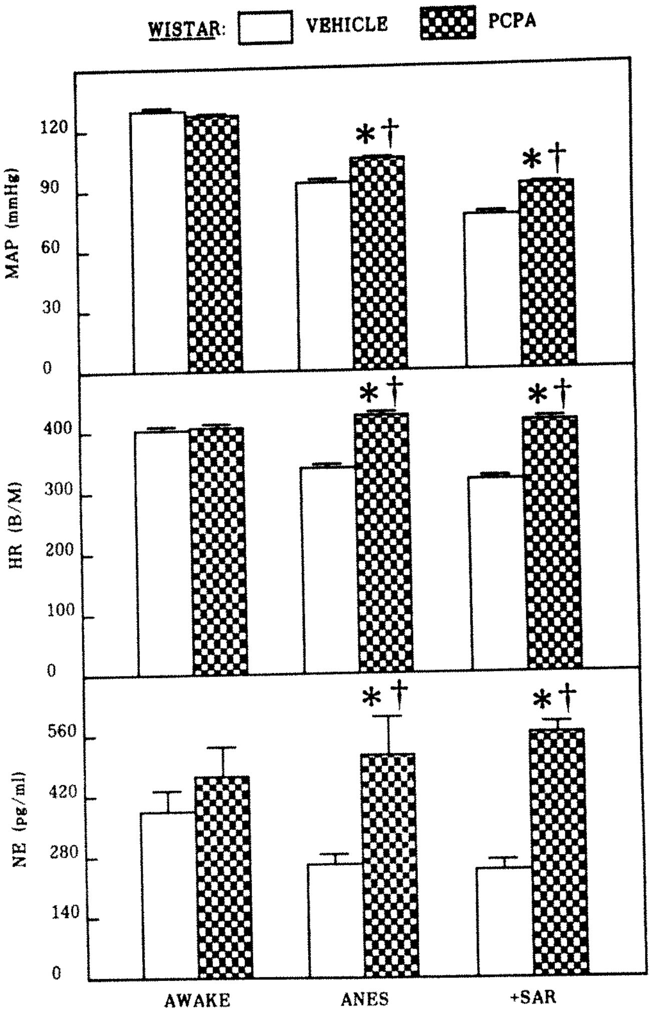


Figure 1. Mean arterial pressure (MAP), heart rate (HR), and plasma norepinephrine (NE) responses in normotensive Wistar rats during the awake period, anesthetized with 2.2% inspired enflurane (ANES) and 2.2% enflurane plus saralasin (+SAR). Vehicle-treated rats ($n = 6$) received saline and PCPA-treated rats ($n = 6$) received 200 mg·kg$^{-1}$ of PCPA intraperitoneally, two days prior to experimentation. The (*) denotes significant differences by unpaired $t$-test and (†) by ANCOVA between vehicle-treated and PCPA-treated rats at the experimental periods. Means ± SEM.

## Methods

### *Laboratory Animals*

Two strains of rats were used. Male Wistar rats served as normotensive controls. Male Wistar rats (150 g) were also used as a model of renovascular hypertension by the method of Goldblatt et al. (17). In this procedure, rats were anesthetized with diethyl ether, the left kidney exposed through a flank incision, and a 0.1-mm silver clip was placed on the renal artery. The other kidney was left undisturbed. Spontaneously hypertensive male rats (SHR) were purchased commercially (Charles River Laboratories) and served as a hypertensive model derived from a strain of rats distinct from Wistar rats.

Experiments were performed on all rats weighing between 250–300 g. In cases of hypertension, only rats with a mean arterial pressure (MAP) of 140 mm Hg or greater were selected for further study. Two rats were selected 48 hr prior to each experiment. One animal was given a single injection of PCPA methyl ester (200 mg·kg$^{-1}$ intraperitoneally); and the other, a single injection of the saline vehicle (intraperitoneally).

### *Experimental Protocol*

Rats were anesthetized briefly with diethyl ether, and a femoral artery and vein were cannulated with PE-50 tubing. The cannulae were exteriorized and flushed with a solution of heparin and physiologic saline. The rats were placed in restraining cages (Braintree Scientific Inc.) for at least 1 hr in order to allow recovery from anesthesia. Blood pressure, which was monitored continuously through the arterial cannula by a Statham P23db pressure transducer using a Brush Mark 2400 recorder, had stabilized well before the end of the recovery period, and the animals were awake and alert.

The protocol consisted of a 60-min awake period, a 20-min anesthetic induction with enflurane (ENF), 60 min of stable anesthesia (2.2% inspired ENF), and a 30-min infusion of saralasin. All animals breathed room air spontaneously throughout the experiment.

In order to ensure a large excess of saralasin relative to angiotensin II at the angiotensin binding sites, an initial dose of saralasin, 100 μg·kg$^{-1}$·min$^{-1}$, dissolved in 0.9 saline solution was infused intravenously, and the infusion was maintained at 10 μg·kg$^{-1}$·min$^{-1}$ for the next 30 min (18). The volume of saralasin administered did not exceed 0.2 ml.

Immediately prior to anesthesia and also 1 hr after stable anesthesia, 1.5 ml of blood was drawn for determination of plasma renin activity (PRA) and plasma catecholamines. A third arterial blood sample was drawn at the end of the infusion for determination of PRA, plasma catecholamines, and arterial blood gases. The sampled blood was centrifuged and plasma withdrawn. The red blood cells remaining were gently

Table 1. Central Bioamine Concentrations (ng/g) in Wistar Rats Treated with Vehicle or PCPA

| Bioamine:treatment | Cord | Medulla | Hypothalamus |
|---|---|---|---|
| 5-HT:vehicle | 505 ± 30 | 783 ± 50 | 927 ± 89 |
| 5-HT:PCPA | 65 ± 13$^a$ | 179 ± 32$^a$ | 173 ± 39$^a$ |
| NE:vehicle | 212 ± 20 | 350 ± 16 | 702 ± 29 |
| NE:PCPA | 204 ± 20 | 355 ± 101 | 649 ± 66 |
| EPI:vehicle | 2 ± 1 | 4 ± 1 | 6 ± 1 |
| EPI:PCPA | 1 ± 1 | 5 ± 1 | 8 ± 1 |
| DA:vehicle | 26.3 ± 2.0 | 39.7 ± 4.3 | 325 ± 81 |
| DA:PCPA | 32.8 ± 4.4 | 42.0 ± 2.0 | 345 ± 78 |

$^a P < 0.05$ by unpaired $t$-test.
Abbreviations: DA, dopamine.

Table 2. Values for Plasma Epinephrine, Plasma Renin Activity, Blood Gases, and Blood pH in Wistar Rats Treated with Vehicle or PCPA

| Sample:treatment | Awake | Anesthetized | + Saralasin |
|---|---|---|---|
| EPI(pg/ml):vehicle | 217 ± 62 | 145 ± 44 | 136 ± 47 |
| EPI:PCPA | 364 ± 44 | 176 ± 44 | 232 ± 33 |
| PRA(ng/ml/hr): vehicle | 1.13 ± 0.28 | 3.27 ± 1.22 | 34.84 ± 10.15 |
| PRA:PCPA | 0.78 ± 0.10 | 1.75 ± 0.45 | 19.15 ± 9.80 |
| $P_{O_2}$:vehicle | — | — | 62.0 ± 2.1 |
| $P_{O_2}$:PCPA | — | — | 64.0 ± 3.1 |
| $P_{CO_2}$:vehicle | — | — | 33.8 ± 2.2 |
| $P_{CO_2}$:PCPA | — | — | 32.8 ± 1.4 |
| pH:vehicle | — | — | 7.40 ± 0.02 |
| pH:PCPA | — | — | 7.40 ± 0.01 |

$^a P < 0.05$ by unpaired $t$-test.
No significant differences were noted between vehicle-treated and PCPA-treated rats.

suspended in saline equal in volume to the plasma removed and subsequently reinfused to replace the shed blood. Catheters were flushed.

### Dissection of Brain Tissues

Immediately after the conclusion of the protocol, anesthetized rats were slowly infused with a 1-ml solution of 5% $Na_2EDTA$ to control chemical and enzymatic breakdown of bioamines. The spinal cord was severed above the fifth vertebra and the brain and cord were removed intact and chilled. The cord was sectioned away from the medulla, and the medulla and hypothalamus were dissected according to the guidelines of Glowinski and Iversen (19). Tissues were then frozen at −80°C and stored for subsequent analysis.

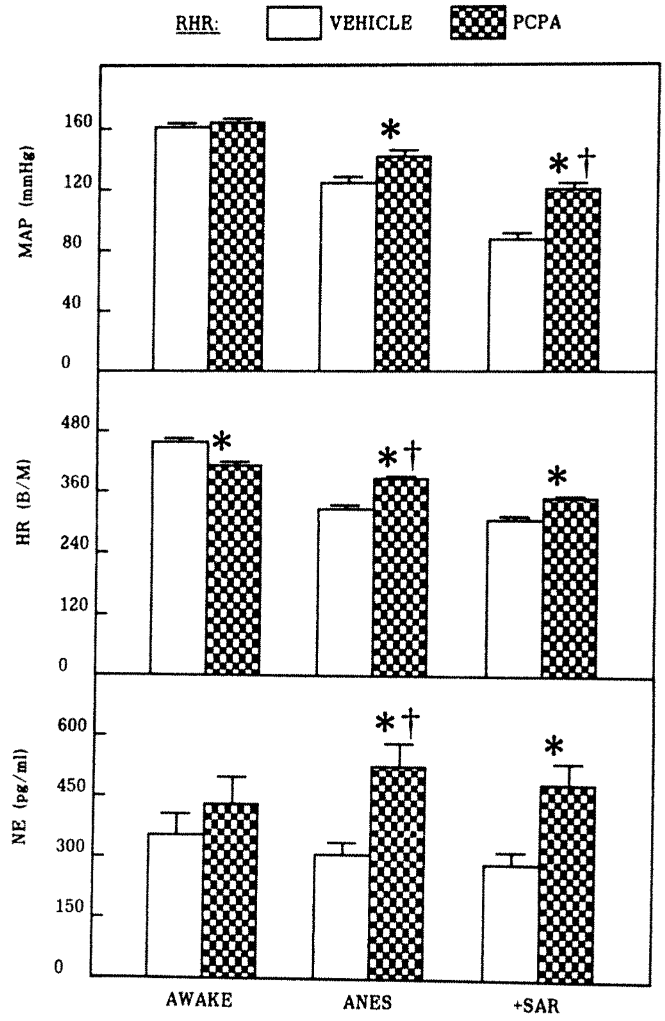


Figure 2. Mean arterial pressure (MAP), heart rate (HR), and plasma norepinephrine (NE) responses in renovascular hypertensive rats (RHR) during the awake period, anesthetized with 2.2% inspired enflurane (ANES) and 2.2% enflurane plus saralasin (+SAR). Vehicle-treated rats ($n = 7$) received saline and PCPA-treated rats ($n = 10$) received 200 mg·kg$^{-1}$ of PCPA intraperitoneally, two days prior to experimentation. The (*) denotes significant differences by unpaired $t$-test and (†) by ANCOVA between vehicle-treated and PCPA-treated rats at the same experimental periods. Means ± SEM.

### Extraction of Tissue

An extraction solution was prepared, composed of 75% ethanol and containing $n$-methylserotonin, an internal standard for 5-HT, and dihydroxybenzylamine, an internal standard for catecholamines. Frozen tissues were weighed and added to test tubes containing 1 ml of the extraction solution. Samples were homogenized using a Brinkman polytron, and centrifuged. A 200-$\mu$l aliquot of the supernatant was obtained for determination of 5-HT content. One ml of 0.1N perchloric acid was added back to the pellet, mixed with the supernatant remaining, and centri-

Table 3. Central Bioamine Concentrations (ng/g) in Renovascular Hypertensive Rats Treated with Vehicle or PCPA

| Bioamine:treatment | Cord | Medulla | Hypothalamus |
|---|---|---|---|
| 5-HT:vehicle | 704 ± 147 | 854 ± 70 | 926 ± 84 |
| 5-HT:PCPA | 129 ± 32[a] | 231 ± 17[a] | 141 ± 17[a] |
| NE:vehicle | 339 ± 96 | 492 ± 23 | 533 ± 31 |
| NE:PCPA | 213 ± 27 | 390 ± 16[a] | 530 ± 53 |
| EPI:vehicle | 6 ± 2 | 6 ± 1 | 5 ± 1 |
| EPI:PCPA | 4 ± 1 | 5 ± 1 | 5 ± 1 |
| DA:vehicle | 84 ± 23 | 91 ± 8 | 385 ± 119 |
| DA:PCPA | 61 ± 20 | 67 ± 15 | 361 ± 69 |

[a] $P < 0.05$ by unpaired $t$-test.
Abbreviations: DA, dopamine.

fuged. The supernatant from this step was decanted and used for the determination of catecholamine content.

### *Assay for Serotonin (5-HT)*

Serotonin was assayed by high performance liquid chromatography in a modified procedure of Lyness et al. (20). Briefly, the ethanolic brain extract was loaded onto a small column containing Bio Rad cation exchange resin. The resin was washed with 0.02 M phosphate buffer, washed with distilled $H_2O$, and eluted with 2M $(NH_4)_2SO_4$ to deadsorb 5-HT. A 200-$\mu$l aliquot of the eluate was injected onto an octyldodecylsilane (ODS) column. Serotonin and its internal standard were resolved and detected electrochemically with a 50 pg sensitivity threshold. Intra- and interassay variability was less than 5 and 10%, respectively.

### *Assay for Catecholamines*

Catecholamines were assayed by high-performance liquid chromatography after the procedure of Woodside et al. (11). Blood samples for analysis of catecholamines were collected in iced polystyrene tubes containing $Na_2EDTA$. After centrifugation, 500 $\mu$l of plasma was collected and stored at −80°C for later analysis. Plasma and brain samples were processed by isolating catecholamines for analysis. Briefly, eight picomoles of internal standard were added to each 500-$\mu$l plasma sample; and catecholamines from both plasma and brain samples were adsorbed to alumina under alkaline conditions. Catecholamines were then eluted with 200 $\mu$l of 0.1N perchloric acid. This eluate was injected and separated by a 5-$\mu$m ODS column. Catecholamines were detected electrochemically with a 30-pg sensitivity threshold. Intra- and interassay variability was less than 5 and 10%, respectively.

Table 4. Values for Plasma EPI, Plasma Renin Activity, Blood Gases, and Blood pH in Renovascular Hypertensive Rats Treated with Vehicle or PCPA

| Sample:treatment | Awake | Anesthetized | + Saralasin |
|---|---|---|---|
| EPI(pg/ml):vehicle | 485 ± 121 | 286 ± 73 | 353 ± 92 |
| EPI:PCPA | 560 ± 137 | 477 ± 80 | 565 ± 53 |
| PRA(ng·ml$^{-1}$·hr$^{-1}$): vehicle | 7.63 ± 3 | 9.54 ± 5 | 32.38 ± 11 |
| PRA:PCPA | 6.14 ± 3 | 5.92 ± 2 | 35.37 ± 8 |
| $P_{O_2}$:vehicle | — | — | 62.4 ± 3.0 |
| $P_{O_2}$:PCPA | — | — | 65.2 ± 2.8 |
| $P_{CO_2}$:vehicle | — | — | 35.6 ± 3.3 |
| $P_{CO_2}$:PCPA | — | — | 33.2 ± 1.7 |
| pH:vehicle | — | — | 7.39 ± 0.02 |
| pH:PCPA | — | — | 7.40 ± 0.02 |

### *Assay of Plasma Renin Activity*

Plasma renin activity (PRA) was estimated, using 0.2 ml of plasma, by a slight modification of the procedure described by Haber et al. using New England Nuclear reagents (21). The plasma was incubated for 2 hr to generate angiotensin I, which was estimated by radioimmunoassay, and the renin activity calculated as ng·ml$^{-1}$·hr$^{-1}$. The plasma samples from the three groups were assayed randomly in nine separate renin assays. Standard curves were constructed in triplicate, and all samples were assayed in duplicate.

### *Statistics*

The data presented are the mean values ± standard error of the mean for two drug treatment groups (vehicle or PCPA) during three experimental periods (awake, anesthetized, or anesthetized plus saralasin infusion) in three rat models (Wistar, RHR, or SHR). Statistically significant differences ($P < 0.05$) were determined using an unpaired $t$-test between vehicle-treated and PCPA-treated groups. In order to determine whether significant differences observed during the anesthetized or anesthetized plus saralasin experimental periods were dependent on the results of previous experimental periods, analysis of covariance (ANCOVA) was also used to determine significant differences ($P < 0.05$) between vehicle-treated and PCPA-treated groups.

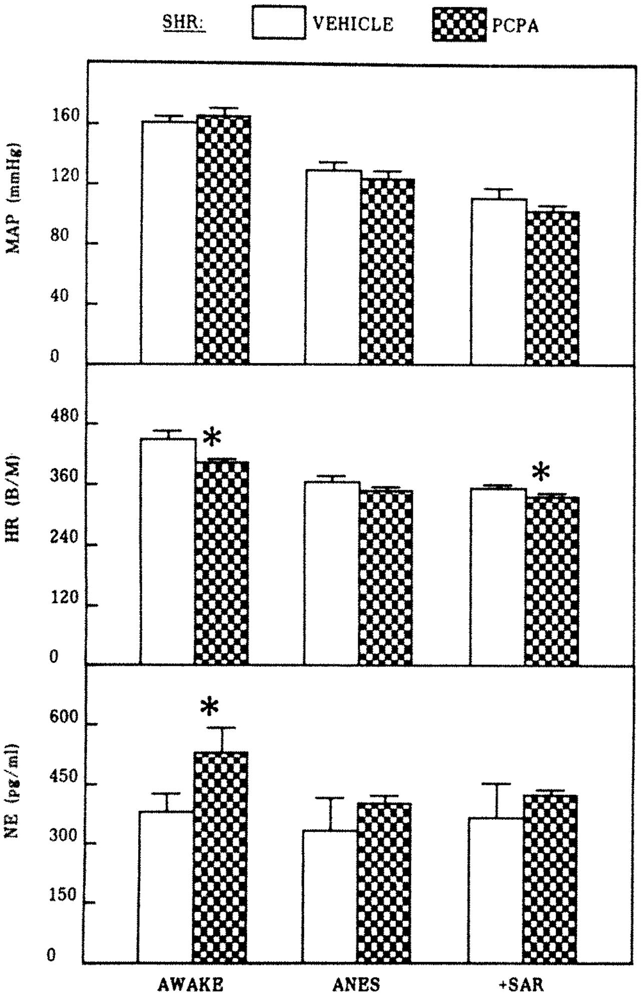


Figure 3. Mean arterial pressure (MAP), heart rate (HR), and plasma norepinephrine (NE) in spontaneously hypertensive rats (SHR) during the awake period, anesthetized with 2.2% inspired enflurane (ANES) and 2.2% enflurane plus saralasin (+SAR). Vehicle-treated rats ($n = 10$) received saline and PCPA-treated rats ($n = 9$) received 200 mg·kg$^{-1}$ of PCPA intraperitoneally, two days prior to experimentation. The (*) denotes significant differences by unpaired $t$-test and (†) by ANCOVA between vehicle-treated and PCPA-treated rats at the same time periods. Means ± SEM.

Table 5. Central Bioamine Concentrations (ng/g) in SHR Rats Treated with Vehicle or PCPA

| Bioamine:treatment | Cord | Medulla | Hypothalamus |
|---|---|---|---|
| 5-HT:vehicle | 695 ± 48 | 887 ± 97 | 1133 ± 61 |
| 5-HT:PCPA | 106 ± 46[a] | 118 ± 26[a] | 173 ± 133[a] |
| NE:vehicle | 338 ± 14 | 496 ± 17 | 664 ± 49 |
| NE:PCPA | 265 ± 10[a] | 515 ± 18 | 736 ± 41 |
| EPI:vehicle | 3 ± 1 | 7 ± 1 | 10 ± 2 |
| EPI:PCPA | 3 ± 1 | 5 ± 1 | 6 ± 1 |
| DA:vehicle | 41 ± 3 | 62 ± 6 | 392 ± 91 |
| DA:PCPA | 60 ± 9[a] | 64 ± 6 | 515 ± 126 |

[a] $P < 0.05$ by unpaired $t$-test.
Abbreviations: DA, dopamine.

## Results

### *Wistar Rats*

Hemodynamic and sympathetic activity were evaluated in Wistar rats during an awake period, after one hour of anesthesia, and during anesthesia with saralasin by measuring mean arterial pressure (MAP), heart rate (HR), and plasma norepinephrine (NE) (Fig. 1). During the awake control period there were no significant differences between the treated and untreated rats in any of these variables. However, during anesthesia there were significant ($P < 0.05$) increases in MAP, HR, and plasma NE in rats treated with PCPA compared to rats treated with vehicle. In addition, the differences during the anesthetic periods remained significant ($P < 0.05$) when tested by ANCOVA, indicating that significance resulted independently of the starting values of the awake experimental period. The combined effects of anesthesia plus saralasin infusion (+ SAR) are also illustrated in Figure 1. The data again showed that MAP, HR, and plasma NE were increased ($P < 0.05$) with PCPA compared to vehicle control. Significance by ANCOVA indicated that differences ($P < 0.05$) were independent of the starting values of the previous anesthetic experimental period.

The effectiveness of the PCPA treatment in Wistar rats is shown in Table 1. Serotonin and catecholamines were measured in the cord (C-1-5), medulla, and hypothalamus. Serotonin was depleted greater than 75% in all three regions of the central nervous system. For catecholamines, tissue concentration in PCPA-treated rats was not different from vehicle-treated controls. The results show that in the CNS, the PCPA treatment that we used specifically depletes stores of 5-HT but not stores of catecholamines.

Blood pH, blood-gas tensions, and other hormones were monitored to determine whether other physiologic conditions were altered by the PCPA treatment. The increases in HR, MAP, and plasma NE in PCPA-treated rats could not be correlated to nonsignificant changes in blood pH, blood-gas tension, plasma epinephrine (EPI), or PRA (Table 2). In all cases, values for PCPA-treated animals were not statistically different from their vehicle-treated counterparts.

### *Renovascular Hypertensive Rats*

Vehicle-treated one-kidney, one-clip, Goldblatt hypertensive rats responded in a manner similar to normotensive rats (Fig. 2). The PCPA-treated RHR had similar MAP and plasma NE to vehicle-treated rats in

Table 6. Values for Plasma EPI, Plasma Renin Activity (PRA), Blood Gases, and Blood pH in SHR Rats Treated with Vehicle or PCPA

| Sample:treatment | Awake | Anesthetized | + Saralasin |
|---|---|---|---|
| EPI(pg/ml):vehicle | 808 ± 204 | 437 ± 44 | 552 ± 47 |
| EPI:PCPA | 616 ± 132 | 409 ± 48 | 520 ± 65 |
| PRA($ng \cdot ml^{-1} \cdot hr^{-1}$): vehicle | 1.59 ± 0.14 | 2.59 ± 0.83 | 18.69 ± 5.91 |
| PRA:PCPA | 1.66 ± 0.17 | 2.25 ± 0.32 | 34.41 ± 6.36 |
| $Po_2$:vehicle | — | — | 63.1 ± 2.1 |
| $Po_2$:PCPA | — | — | 66.4 ± 1.5 |
| $Pco_2$:vehicle | — | — | 30.2 ± 2.1 |
| $Pco_2$:PCPA | — | — | 30.5 ± 1.0 |
| pH:vehicle | — | — | 7.43 ± 0.02 |
| pH:PCPA | — | — | 7.42 ± 0.01 |

the awake state. Heart rate was significantly lower at this time. With enflurane anesthesia and enflurane anesthesia plus saralasin, MAP, HR, and plasma NE were significantly greater in the PCPA-treated RHR compared to the vehicle-treated RHR. Statistical tests by ANCOVA indicated that the difference ($P < 0.05$) in MAP with anesthesia was not independent of the starting MAP values of the awake period; however, the difference ($P < 0.05$) in MAP with saralasin was independent of the starting MAP values during anesthesia. In terms of HR and plasma NE, differences noted during anesthesia were independent ($P < 0.05$) of awake starting values, but differences with saralasin were not independent of anesthetized starting values.

Analysis of central serotonin in the RHR shows that PCPA depletion of 5-HT in the cord, medulla, and hypothalamus was 73% or greater (Table 3). In nine measurements of central catecholamine concentrations, only NE in the medulla was significantly decreased with PCPA. The central depletion of 5-HT did not affect blood pH, blood-gas tension, or other measured hormones. The PCPA-treated RHR was not different from the vehicle-treated RHR in this regard (Table 4).

### *Spontaneously Hypertensive Rats*

As with RHR, only SHR having MAP values of 140 mm Hg or greater were used in experiments. The experimental protocol was identical to that previously stated for Wistar and RHR. Figure 3 shows that the SHR deviate from the trends established for Wistar and RHR. During enflurane anesthesia and anesthesia with saralasin infusion, SHR depleted of serotonin did not exhibit the same responses in terms of MAP, HR, and plasma NE that Wistar or RHR did. Figure 3 shows that the mean values of MAP and HR of PCPA-treated rats are statistically less than or not different from the mean values of rats treated with vehicle.

Serotonin was depleted in the SHR comparable to Wistar and RHR treated similarly (Table 5). Tissue catecholamines in the PCPA-treated SHR were mildly affected. Tissue NE was slightly elevated and tissue dopamine was decreased in the cord only (Table 5). There was no other evidence that PCPA altered central catecholamine concentrations. Nonsignificant changes in blood pH, blood-gas tension, plasma EPI, and PRA did not explain the differences seen between Wistar rats and SHR (Table 6).

## Discussion

In a review by Kuhn et al. (22), several studies indicated that the level of depletion with PCPA achieved in our study (>70%) was sufficient to alter the hemodynamic properties of the rat model. However, the precise way in which this depletion might alter hemodynamic function was difficult to determine given that 5-HT receptors are associated with both pressor and depressor responses (23–25). The nonselective depletion of 5-HT by PCPA will no doubt affect both of these systems. At this juncture however, we were not concerned with the complex pharmacodynamic changes in neuronal pathways of the rat model after treatment with PCPA but only with net difference between state 1 (vehicle treatment) and state 2 (PCPA treatment). Measurements related to this objective will answer the simple but important question of whether or not the 5-HT neuronal network in total is important during anesthesia.

One important aspect of our study was to examine animals awake prior to enflurane anesthesia. Awake animals depleted of central serotonin had hemodynamic and hormonal values similar to vehicle-treated rats. This observation at first appeared to dispute the findings of Ito and Schamberg (26) who showed that awake rats treated with PCPA had significantly higher blood pressures than normal. However, on closer inspection, the disparity in results might be explained by several major differences in methodology. First, Sprague–Dawley rats weighing between 140 and 160 g used by Ito and Schamberg have different cardiovascular properties than our strains (Wistar and SHR) weighing between 250–300 g. Second, Ito and Schamberg reported systolic pressures by a tail–plethysmographic cuff method rather than by measuring MAP continuously with a Statham P23db pressure transducer as we preferred. Finally, they report a hypertension latency threshold of two days in their rat model after PCPA at 200 mg/kg intraperitoneally. We also used this milder treatment to ensure catecholamine integrity in the CNS. However, given our rat models, we proceeded with experiments even though a hypertensive state in terms of MAP was not reached at this time in the awake state.

During enflurane anesthesia, the Wistar rat was apparently more sensitive to the cardiovascular effects of this PCPA treatment and exhibited a relative hypertensive condition compared to vehicle control. In these rats, whether normotensive or hypertensive, there was an increase in heart rate, blood pressure, and plasma norepinephrine with PCPA compared to control during enflurane anesthesia. That the increase in sympathetic tone as reflected by plasma norepinephrine was due to serotonin depletion and not to a cocaine-like effect of PCPA was supported by normal brain catecholamine concentrations. The fact that plasma epinephrine and plasma renin activity respond similarly in treated and untreated rats suggests that central serotonergic nerves do not influence directly renin release or release of epinephrine from the adrenal gland.

The obvious difference in response to enflurane seen in the SHR as compared to Wistar rats suggests that the serotonin component of blood pressure control is different. Pilot studies concerning the cardiovascular effects of PCPA on the Wistar–Kyoto rat (the genetic normotensive control for the SHR) were discontinued because they gave similar results to the normotensive Wistar rat. Elevation in arterial blood pressure alone was not responsible for the differences seen because the RHR responded in a manner similar to the normotensive Wistar rat. Several studies suggest that the SHR has several central nervous system components that are different from normotensive Wistar rats (27,28). It would appear that serotonin plays an insignificant role in blood pressure support in SHR anesthetized with enflurane.

The precise manner in which enflurane interacts with serotonin to reduce peripheral sympathetic activity is unknown. Diaz et al. (29) have examined turnover rates of serotonin in the presence of several inhalational anesthetics. Cerebral content of serotonin increased slightly with cyclopropane, decreased with halothane, and did not change with diethyl ether. In another study, Roizen et al. (30) showed that the use of halothane and cyclopropane was associated with the accumulation of serotonin in several brain tissues known to contain serotonergic neurons. Although these studies demonstrate potentially important effects of anesthetics on serotonin, they do not describe the dynamic properties of release from neurons. Further studies are necessary to allow quantification of dynamic events with different neurotransmitters. Certainly the hemodynamic and hormonal responses seen with a variety of anesthetic agents are modified by how anesthetic agents affect central neurotransmitter function.

In conclusion, the depletion of serotonin from CNS regions results in higher heart rate, blood pressure, and plasma norepinephrine in normotensive Wistar rats and Wistar rats with renovascular hypertension during enflurane anesthesia. SHR do not respond in a similar manner. The data suggest that peripheral sympathetic activity, as measured by plasma norepinephrine, is partially influenced by central serotonin content. Enflurane anesthesia appears to decrease peripheral sympathetic tone, in part by altering central serotonergic function.

## References

1. Price ML, Price HL. Effects of general anesthetics on contractile response of rabbit aortic strips. Anesthesiology 1962;23:16–20.
2. Merin RG. Inhalation anesthetics and myocardial metabolism: possible mechanisms of functional effects. Anesthesiology 1973;39:216–55.
3. Kortly KJ, Ebert TJ, Vucins EJ, Igler FO, Barney JA, Kampine JP. Baroreceptor reflex control of heart rate during isoflurane anesthesia in humans. Anesthesiology 1984;60:173–9.
4. Roizen MF, Moss J, Henry DP, Kopin IJ. Effects of halothane on plasma catecholamines. Anesthesiology 1974;41:432–9.
5. Philbin DM, Coggins CH. Plasma antidiuretic hormone levels in cardiac surgical patients during morphine and halothane anesthesia. Anesthesiology 1978;49:95–8.
6. Berman ML, Green OC. Acute stimulation of cortisol metabolism by pentobarbital in man. Anesthesiology 1971;34:365–9.
7. Ngai SH, Cheney DL, Finck AD. Acetylcholine concentrations and turnover in rat brain structures during anesthesia with halothane, enflurane and ketamine. Anesthesiology 1978;48:4–10.
8. Miller ED, Longnecker DE, Peach MJ. The regulatory function of the renin-angiotensin system during general anesthesia. Anesthesiology 1978;48:399–403.
9. Miller ED, Gianfagna W, Ackerly JA, Peach MJ. Converting-enzyme activity and pressor responses to angiotensin I and II in the rat awake and during anesthesia. Anesthesiology 1979;50:88–92.
10. Miller ED, Beckman JJ, Woodside JR, Althaus JS, Peach MJ. Blood pressure control during anesthesia: importance of the peripheral sympathetic nervous system and renin. Anesthesiology 1983;58:32–7.
11. Woodside JR, Beckman JJ, Althaus JS, Miller ED. Central depletion of catecholamines: importance of hypertension and anesthesia. Anesth Analg 1984;63:482–8.
12. DeJong W, Nijkamp FP, Bohus B. Role of noradrenaline and serotonin in the central control of blood pressure in normotensive and spontaneously hypertensive rats. Arch Int Pharmacodyn Ther 1975;213:272–84.
13. Neumayer RJ, Hare BD, Franz DD. Evidence for bulbospinal control of sympathetic preganglionic neurons by monoaminergic pathways. Life Sci 1974;14:793–806.

14. Coote JH, MacLeod VH. The influence of bulbospinal monaminergic pathways on sympathetic nerve activity. J Physiol (Lond) 1974;241:453–75.
15. Wolf WA, Kuhn DM, Lovenberg W. Pressor effects of dorsal raphe stimulation and intrahypothalamic application of serotonin in the spontaneously hypertensive rat. Brain Res 1981;208:192–7.
16. Koe BK, Weissman A. P-chlorophenylalanine: a specific depletor of brain serotonin. J Pharmacol Exp Ther 1966;154:499–506.
17. Goldblatt HJ, Lynch RF, Hanzal RF, Summerville WW. Studies on experimental hypertension I. The production of persistent elevation of systolic blood pressure by means of renal ischemia. J Exp Med 1934;59:347–54.
18. Isikawa I, Hollenberg N. Blockage of the systemic and renin vascular actions of angiotensin II with 1-sar, 8-ala analogue in the rat. Life Sci 1975;17:121–30.
19. Glowinski J, Iversen LL. Regional studies of catecholamines in the rat brain. J Neurochem 1966;13:655–69.
20. Lyness WH, Friedle NM, Moore KE. Measurement of 5-hydroxytryptamine and 5-hydroxyindoacetic acid in discrete brain nuclei using reverse phase liquid chromatography with electrochemical detection. Life Sci 1980;26:1109–14.
21. Haber E, Koerner T, Page LB, Klemin B, Purnode A. Application of radioimmunoassay or angiotensin I to the physiologic measurements of plasma renin activity in normal human subjects. J Clin Endocrinol Metab 1969;29:1349–55.
22. Kuhn DM, Wolf WA, Lovenberg W. Review of the role of the central serotonergic neuronal system in blood pressure regulation. Hypertension 1980;2:243–55.
23. Coote JH, MacLeod VH. The influence of bulbospinal monoaminergic pathways on sympathetic nerve activity. J Physiol (Lond) 1974;241:453–75.
24. Koss MC, Wang SC. Brainstem loci for sympathetic activation of the nictitating membrane and pupil in the cat. Am J Physiol 1972;222:900.
25. Neumayer RJ, Hare BD, Franz DN. Evidence for bulbospinal control of sympathetic preganglionic neurons by monoaminergic pathways. Life Sci 1974;14:793–806.
26. Ito A, Schamberg SM. Central nervous system mechanisms responsible for blood pressure elevation induced by P-chlorophenylalanine. J Pharmacol Exp Ther 1972;181:65–74.
27. Saavedra JM, Grobecker H, Axelrod R. Changes in central catecholaminergic neurons in the spontaneously (genetic) hypertensive rat. Circ Res 1978;42:529–34.
28. Nagatsu T, Ikuta K, Numata Y, Kata T, Sano M, Nagatsu I, Umezawa H, Matsuzaki M, Takeuchi T. Vascular and brain dopamine-B-hydroxylase activity in young spontaneously hypertensive rats. Science 1976;191:290–1.
29. Diaz PM, Ngai SH, Costa E. The effects of cyclopropane, halothane and diethyl ether on the cerebral metabolism of serotonin in the rat. Anesthesiology 1968;29:959–63.
30. Roizen MF, Kopin IJ, Palkovitz M, Brownstein M, Kizer JS, Jacobowitz DM. The effect of two diverse inhalational anesthetic agents on serotonin in discrete regions of the rat brain. Exp Brain Res 1975;24:203–7.

ANESTH ANALG 1171
1985;64:1171–7

# Transient Inhibitory Effect of Isoflurane upon Oxidative Halothane Metabolism

Vera Fiserova-Bergerova, PhD, and Damian F. Dolan, BS

FISEROVA-BERGEROVA V, DOLAN DF. Transient inhibitory effect of isoflurane upon oxidative halothane metabolism. Anesth Analg 1985;64:1171–7.

*The duration of inhibition of halothane oxidative metabolism by isoflurane was studied in rats exposed for 2 hr to an anesthetic concentration of isoflurane (0.6% inspired), followed by a 2-hr exposure to a subanesthetic concentration of halothane (0.06% inspired), starting either 0.5, 4, or 24 hr after the end of the isoflurane exposure. Other rats were exposed to halothane, isoflurane, or a mixture of both. Tissue levels of total nonvolatile fluorine were used as a measure of oxidative metabolism of halothane and hepatic levels of 1,1,1-trifluoro-2-chloroethane and 1,1-difluoro-2-chloroethylene as a measure of reductive metabolism of halothane. Isoflurane administered simultaneously with or 30 min prior to halothane significantly inhibited oxidative metabolism of halothane, but this inhibition was transient and was no longer apparent when halothane was administered 4 or 24 hr after the end of isoflurane anesthesia. The reductive metabolism of halothane was unaffected. This study suggests that isoflurane may transiently modify the action of some drugs administered during the perianesthesia period by inhibiting their oxidative metabolism. Differences in elimination kinetics of nonvolatile fluorine-containing metabolites after isoflurane and halothane exposure suggest the presence of an unidentified isoflurane metabolite.*

Key Words: ANESTHETICS—volatile, halothane, isoflurane. BIOTRANSFORMATION (DRUG)—halothane, isoflurane. PHARMACOKINETICS—halothane, isoflurane.

The metabolism of many xenobiotics may be altered by inhalation exposure of a variety of chemical substances (1–3), including inhalation anesthetics (4,5). In an earlier study, we demonstrated that when isoflurane is inhaled at subanesthetic concentrations, the oxidative metabolism of halothane is inhibited in a concentration-dependent manner (4). Because isoflurane is used during clinical anesthesia, its interaction with drug metabolism may modify the action of drugs administered during the perianesthesia period. In the following study the duration of the inhibitory effect of isoflurane on halothane metabolism was investigated. The increase in concentration of total nonvolatile fluorine in tissues above background levels has been used as a measure of the oxidative metabolism of halothane and hepatic concentrations of 1,1,1-trifluoro-2-chloroethane (TFE) and 1,1-difluoro-2-chloroethylene (DFE) as measures of reductive metabolism of halothane (4). Because the ratio between oxidative and reductive metabolism of halothane depends upon the concentration of oxygen (6,7) and halothane (8) in the inhaled mixture, the concentrations of oxygen and halothane in the exposure chamber were maintained at 21 and 0.06%, respectively. Because total nonvolatile fluorine in liver increased significantly during isoflurane anesthesia, the tissue clearance of nonvolatile fluorine after isoflurane anesthesia was also studied.

## Material and Methods

### Reagents

Halothane was purchased from Ayerst Laboratories, NY. Isoflurane was provided by Ohio Medical Products. TFE and DFE were obtained from PCR Research Chemicals, Inc., Gainesville, FL.

### Animal Exposures

The experimental animals were female Sprague–Dawley rats (weighing approximately 200 g each) received in two shipments from the Charles River Laboratories, 3 months apart. They were kept on a diet of standard Purina Lab Chow and water ad libitum. Rats used in experiments 1 and 2 were from the first

---

This study was supported by Ohio Medical Products and NIH grant ES 01029-08.

Received from the Department of Anesthesiology, University of Miami School of Medicine, Miami, Florida. Accepted for publication June 24, 1985.

Address correspondence to Dr. Fiserova-Bergerova (Thomas), Department of Anesthesiology R-9, University of Miami School of Medicine, PO Box 016370, Miami, FL 33101.

© 1985 by the International Anesthesia Research Society

Table 1. Isoflurane and Halothane Concentrations in Exposure Chamber and in Tissues of Rats Decapitated at the End of Halothane Exposure

| | Simultaneous exposure | 2.5 hr elapsed[a] | | 6 hr elapsed[a] | | 26 hr elapsed[a] | |
|---|---|---|---|---|---|---|---|
| | | No pretreatment[b] | Isoflurane pretreatment | No pretreatment[b] | Isoflurane pretreatment | No pretreatment[b] | Isoflurane pretreatment |
| Chamber (% vol/vol) | | | | | | | |
| Isoflurane | 0.610 ± 0.019 | 0 | 0.554 ± 0.014 | 0 | 0.554 ± 0.014 | 0 | 0.554 ± 0.014 |
| Halothane | 0.060 ± 0.001 | 0.060 ± 0.002 | 0.060 ± 0.002 | 0.062 ± 0.004 | 0.062 ± 0.004 | 0.057 ± 0.001 | 0.057 ± 0.001 |
| Liver (nmol/g) | | | | | | | |
| Isoflurane | 1113 ± 68 | 0 | 22 ± 2.7 | 0 | 4.8 ± 1.8 | 0 | trace |
| Halothane | 159 ± 11[c] | 90 ± 4 | 102 ± 11 | 99 ± 11 | 91 ± 6 | 102 ± 10 | 103 ± 10 |
| Muscle (nmol/g) | | | | | | | |
| Isoflurane | 389 ± 57 | 0 | 14 ± 2.8 | 0 | 4.6 ± 2.5 | 0 | trace |
| Halothane | 65 ± 7[c] | 49 ± 9 | 50 ± 4 | 50 ± 4 | 54 ± 16 | 53 ± 7 | 34 ± 2 |
| Brain (nmol/g) | | | | | | | |
| Isoflurane | 609 ± 35 | 0 | 7.5 ± 11 | 0 | 1.3 ± 0.3 | 0 | 0 |
| Halothane | 116 ± 10[c] | 82 ± 8 | 88 ± 5 | 86 ± 8 | 77 ± 6 | 84 ± 10 | 85 ± 3 |

$\bar{X} \pm$ SEM, $n = 6$.

[a] Elapsed time indicates how soon after the end of a 2-hr isoflurane preanesthesia rats were decapitated. During the last 2 hr prior to decapitation, nonpretreated control rats and rats previously anesthetized with isoflurane were exposed to halothane.

[b] Control rats previously unexposed to any drug were exposed to halothane at the same time as rats previously anesthetized with isoflurane.

[c] Halothane content is significantly larger than halothane content in any other group of rats shown in this table ($P < 0.01$).

shipment, and rats used in experiments 3 and 4 were from the second shipment. To account for variation of fluorine content in tissue caused by dietary and environmental conditions, unexposed rats from each shipment kept under the same regimens as exposed rats served as background controls. For each study the rats were pooled into groups of six so that means and standard deviations of body weights in all groups were similar.

### *The Exposure Chamber*

Rats were exposed in an exposure chamber adapted from a 20-L glovebox (8). The temperature in the exposure chamber varied with room temperature (22–24°C). The oxygen concentration in the chamber, monitored by a model D2 Beckman oxygen analyzer, was 21%. The gas mixture in the exposure chamber was sampled frequently with a 20-ml glass syringe from two places near the respiratory zone of the rats. The desired concentrations of the anesthetics were reached within the first 10 min of exposure. During the remainder of the exposure period the concentration in the exposure chamber fluctuated less than 5% of the mean value. The means and standard errors of time weighted average for each study are given in Tables 1 and 3. Exposed rats were decapitated inside the exposure chamber; selected tissues were immediately excised outside the exposure chamber and prepared for analysis. Rats were exposed in small groups to minimize postmortem metabolism of halothane. Samples of tissue were frozen and later analyzed for total nonvolatile fluorine. Femurs and tibias stripped of flesh were used for measurement of osseous concentrations of fluoride.

Rats were exposed as follows:

1) *Simultaneous exposure to isoflurane and halothane.* Two rats exposed to air containing 0.6% isoflurane (vol/vol) and 0.06% halothane (vol/vol) for 2 hr were decapitated within the exposure chamber. Two unexposed rats served as controls. The experiment was repeated three times.
2) *Successive exposures to isoflurane and halothane.* Three rats were exposed for 2 hr to 0.6% isoflurane in air, removed from the exposure chamber, and recovered from anesthesia inhaling uncontaminated room air. At the appropriate time (either 30 min, 4 hr, or 24 hr after the end of isoflurane exposure), an isoflurane-exposed rat was paired with an unexposed rat, placed in the exposure chamber, and exposed to 0.06% halothane in air. At the end of this 2-hr halothane exposure, both rats were decapitated inside the exposure chamber. At the same time, one unexposed control rat was decapitated. The experiment was repeated six times.
3) *Exposure to isoflurane only.* Eight rats were exposed at the same time to 0.6% isoflurane in air. At the end of a 2-hr exposure, two rats were decapitated, and the remaining rats were removed from the exposure chamber and recovered from anesthesia

inhaling uncontaminated room air. These rats were decapitated in pairs either 2.5, 6, or 26 hr later. Two unexposed rats served as controls. The experiment was repeated three times.

4) *Exposure to halothane only.* The experimental design was the same as in study 3, but 0.076% halothane was used instead of isoflurane, and the number of rats increased by 6. These additional rats were decapitated 48 hr after halothane exposure.

### *Analytical Procedures*

*Gas analysis.* Concentrations of halothane and isoflurane in the exposure chamber were measured by gas chromatography (4). The analyses were performed on an F & M 402 gas chromatograph equipped with a flame ionization detector and a 1.8-m glass column packed with 10% diisodecylphthalate on Chromosorb P (45–60 mesh) and heated to 65°C. Samples of 50 μl were injected on the gas–chromatographic column with a gas-tight syringe.

*Tissue analysis.* Concentrations of halothane, isoflurane, and volatile metabolites in tissues were determined by gas–chromatographic analysis using the headspace method (8). Approximately 0.5 g of tissue was homogenized in a closed system. (Carbon monoxide was used to prevent postmortem biodegradation.) When the partial pressures of the volatile components were equilibrated, the gas in the headspace of the homogenates was analyzed using a Varian 3700 gas chromatograph equipped with a flame ionization detector and a glass column packed with n-octane on Porasil C (100–120 mesh) and heated to 102°C.

Concentrations of total nonvolatile fluorine were determined in tissues, desiccated at pH 10, and combusted by use of a specific fluoride ion electrode (8). Fluorine released by halothane metabolism was calculated by determining the difference between the fluorine concentration in tissue of a rat exposed to halothane and fluorine concentrations in tissue of an appropriate control rat. Unexposed rats served as controls for rats exposed to halothane only. Rats exposed only to isoflurane and decapitated 0, 2.5, 6, or 26 hr later (study 3) served as controls for preanesthetized rats exposed to halothane.

Concentrations of fluoride in bones also were calculated. Fluoride was extracted in 5% Na-EDTA and determined by use of a specific fluoride ion electrode (9). All tissue analyses were made in duplicate. Differences between measurements rarely exceeded 5% of the mean.

*Statistical analysis.* The significance of differences between means of concentrations in tissues obtained from different groups of rats was tested by the two sample two tailed *t*-test, the paired *t*-test, and by analysis of variance. Inhibition of oxidative metabolism was evaluated from the increase of fluorine concentrations in liver of preanesthetized and control rats exposed to halothane

$$\text{inhibition } \% = 100\left[\frac{H - IH + I - U'_n}{H - U_n}\right]$$

where the letters denote mean concentrations in the following groups: $IH$, rats exposed to isoflurane and halothane (Table 2); $I$, appropriate control rats exposed only to isoflurane (Table 3); $H$, rats exposed to halothane only (Table 2); $U_n$, unexposed control rats (Table 2); $U'_n$, unexposed control rats (Table 3).

## Results

A concentration of 0.6% isoflurane produced light anesthesia; rats responded to tail stimulation but did not respond to noise stimulation. After the end of exposure, the rats required approximately 3 min to regain consciousness and 10–15 min to recover completely from anesthesia. Exposure to 0.06% halothane had no effect on the behavior of the rats.

### *Unexposed Rats*

Unexposed rats had no measurable tissue concentrations of isoflurane, halothane, TFE, or DFE. Concentrations of total nonvolatile fluorine were in the range of normal background levels of unexposed rats, but the levels in the tissues of the rats from the second shipment were higher than the levels in tissues of the rats from the first shipment (Tables 2 and 3). This difference is attributed to the different environmental conditions prior to the time the rats reached our laboratory.

### *Simultaneous Exposure of Isoflurane and Halothane*

Mean concentrations of halothane and isoflurane in tissues of rats exposed simultaneously to isoflurane and halothane are shown in Table 1. Liver, muscle, and brain concentrations of halothane were greater in tissues of rats exposed to halothane in the presence of isoflurane than in rats exposed to halothane alone ($P < 0.01$). Mean concentrations of metabolites in tissues are shown in Table 2. Concentrations of total nonvolatile fluorine in the liver, kidney, muscle, and

Table 2. Concentrations of Halothane Metabolites in Tissues of Rats Decapitated at the End of Halothane Exposure (nmol/g)

| | Unexposed rats[b] | Simultaneous exposure | 2.5 hr elapsed[a] | | 6 hr elapsed[a] | | 26 hr elapsed[a] | |
|---|---|---|---|---|---|---|---|---|
| | | | No pretreatment[c] | Isoflurane pretreatment | No pretreatment[c] | Isoflurane pretreatment | No pretreatment[c] | Isoflurane pretreatment |
| Liver | | | | | | | | |
| DFE | 0 | 2.75 ± 0.20 | 2.80 ± 0.30 | 3.2 ± 0.2 | 3.2 ± 0.4 | 3.3 ± 0.2 | 2.5 ± 0.2 | 2.9 ± 0.2 |
| TFE | 0 | 16.7 ± 1.8 | 20.8 ± 1.8 | 23.0 ± 2.1 | 22.3 ± 2.8 | 21.8 ± 2.2 | 17.3 ± 1.9 | 17.9 ± 1.5 |
| F | 80.1 ± 1.8 | 768 ± 45[d] | 1062 ± 66 | 954 ± 57[e] | 1131 ± 108 | 1185 ± 123 | 1017 ± 84 | 1104 ± 84 |
| Muscle | | | | | | | | |
| F | 60.9 ± 1.8 | 156 ± 12[d] | 264 ± 12 | 285 ± 18 | 345 ± 45 | 309 ± 21 | 312 ± 21 | 318 ± 15 |
| Kidney | | | | | | | | |
| F | 73.2 ± 5.7 | 240 ± 3[d] | 525 ± 60 | 465 ± 33[e] | 630 ± 84 | 543 ± 78 | 513 ± 30 | 534 ± 33 |
| Lung | | | | | | | | |
| F | 57.0 ± 1.8 | 120 ± 6[d] | 414 ± 36 | 387 ± 39[e] | 423 ± 27 | 483 ± 54 | 435 ± 33 | 441 ± 27 |

$\bar{X}$ ± SEM, $n = 6$.

Abbreviations: F, total nonvolatile fluorine; DFE, 1,1-difluoro-2-chloroethylene; TFE, 1,1,-trifluoro-2-chloroethane.

[a] Elapsed time indicates how soon after the end of a 2-hr isoflurane preanesthesia rats were decapitated. During the last 2 hr prior to decapitation, nonpretreated control rats and rats previously anesthetized with isoflurane were exposed to halothane.

[b] $n = 12$ (Because there was no statistically significant difference between tissue concentrations of unexposed control rats in experiments 1 and 2, the data were combined).

[c] Control rats previously unexposed to any drug were exposed to halothane at the same time as rats previously anesthetized with isoflurane.

[d] Fluorine content is significantly different from fluorine content in any other group of rats shown in this table ($P < 0.01$).

[e] Fluorine content is significantly larger than in unexposed rats ($P < 0.01$) but significantly smaller than in control rats exposed only to halothane ($P < 0.05$).

Table 3. Concentrations of Total Nonvolatile Fluorine (nmol/g) in Tissues of Rats Exposed for 2 hr to 0.60% Isoflurane or 0.076% Halothane

| | Unexposed rats | Hours between end of exposure and decapitation | | | | |
|---|---|---|---|---|---|---|
| | | 0 | 2½ | 6 | 26 | 48 |
| 0.60% Isoflurane ($n = 6$; $\bar{X}$ ± SEM) | | | | | | |
| Liver | 118 ± 1 | 606 ± 63 | 161 ± 9 | 155 ± 17 | 159 ± 8 | — |
| Muscle | 91 ± 4 | 134 ± 18 | 100 ± 5 | 98 ± 10[a] | 108 ± 4 | — |
| Kidney | 87 ± 1 | 208 ± 21 | 110 ± 7 | 117 ± 13 | 114 ± 4 | — |
| Lung | 82 ± 5 | 101 ± 14 | 104 ± 6 | 109 ± 13 | 104 ± 3 | — |
| 0.076% Halothane ($n = 6$; $\bar{X}$ ± SEM) | | | | | | |
| Liver | 132 ± 9 | 993 ± 48 | 1164 ± 27 | 963 ± 81 | 603 ± 30 | 360 ± 18 |
| Muscle | 99 ± 9 | 261 ± 18 | 468 ± 9 | 423 ± 54 | 269 ± 15 | 168 ± 12 |
| Kidney | 93 ± 9 | 453 ± 30 | 618 ± 36 | 573 ± 42 | 364 ± 15 | 222 ± 9 |
| Lung | 93 ± 9 | 399 ± 75 | 588 ± 30 | 561 ± 33 | 381 ± 15 | 222 ± 24 |

[a] No statistically significant differences between exposed and unexposed rats. All other differences between exposed and unexposed rats were statistically significant at $P < 0.01$.

lung of rats exposed simultaneously to halothane and isoflurane were signficantly less than concentrations in tissues obtained from rats exposed to halothane alone ($P < 0.01$). The volatile metabolites, TFE and DFE, were found in measurable quantities only in liver tissue. There were no statistically significant differences between concentrations of volatile metabolites in liver obtained from rats exposed simultaneously to halothane and isoflurane and rats exposed to halothane alone. This study shows that isoflurane anesthesia inhibits oxidative metabolism of halothane but has no effect on reductive metabolism of halothane.

### *Successive Exposures to Isoflurane and Halothane*

At the end of a halothane exposure, the concentrations of halothane in tissues of control rats and rats previously anesthetized with isoflurane were the same (Table 1, $P > 0.1$). Concentrations of isoflurane in tissues declined rapidly after isoflurane anesthesia (Table 1). Concentrations of metabolites in tissues are in Table 2. After exposure to halothane, concentrations of total nonvolatile fluorine in liver, lung, and kidney of rats preanesthetized with isoflurane were significantly less than concentrations in tissues of rats untreated with isoflurane when the isoflurane anesthesia and halothane exposure were 30 min apart (paired *t*-test; $P < 0.05$). When the total nonvolatile fluorine released by halothane metabolism was examined by analysis of variance, significant interaction of halothane and isoflurane was indicated ($P < 0.01$). Analysis of variance and paired *t*-test indicated that the concentrations of nonvolatile fluorine in tissues of rats exposed to halothane 4 or 24 hr after isoflurane anesthesia were not significantly different from concentrations in tissues of control rats exposed to halothane alone. DFE and TFE were present in a measurable quantity only in liver tissue of rats exposed to halothane. No statistically significant differences were found in concentrations of these volatile metabolites in liver of rats preanesthetized with isoflurane and in control rats untreated with isoflurane. This study shows that inhibition of oxidative metabolism by isoflurane is reversible and short-lived.

### *Exposure to Isoflurane Only*

After isoflurane anesthesia, tissue concentrations of nonvolatile fluorine were greater than concentrations in unexposed rats but less than in rats exposed to halothane (Table 3). The concentrations in liver tissue were much larger than concentrations in other tissues. All differences were statistically significant ($P < 0.01$). The concentrations of the fluorine-containing metabolites in all tissues rapidly decreased immediately after the end of isoflurane exposure (approximately 90% of flourine generated by isoflurane metabolism was removed from the liver during the 2.5 hr after exposure). After 2.5 hr, the elimination rate becomes very slow, as indicated by the statistically significant increased concentrations of nonvolatile fluorine in tissues even 26 hr after exposure. This study shows that significant amounts of fluorine-containing metabolites are formed during isoflurane anesthesia and that elimination of these metabolites is biphasic (Fig. 1).

### *Exposure to Halothane Only*

After exposure to halothane, concentrations of nonvolatile fluorine were significantly increased in all tissues and remained significantly elevated for 48 hr after exposure (Table 3). Fluorine concentrations in all tissues declined exponentially, with half-times of approximately 20 hr (Fig. 1). This study shows that the kinetics of elimination of nonvolatile fluorine metabolites from halothane and isoflurane are different.

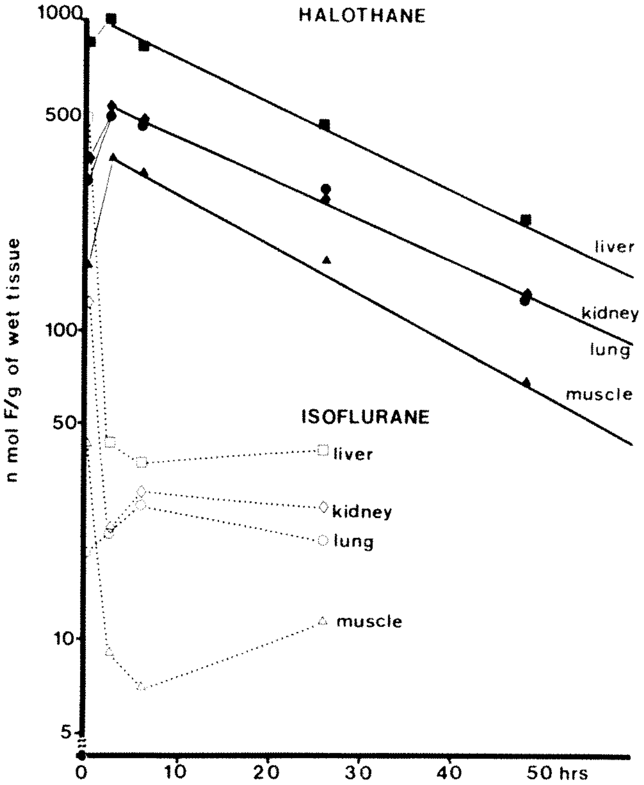


Figure 1. Elimination of nonvolatile fluorine from tissues of rats after exposure to halothane or isoflurane. Rats exposed for 2 hr to either 0.076% (vol/vol) halothane or 0.6% (vol/vol) isoflurane were sacrificed at prescheduled times. The concentration increase of nonvolatile fluorine (determined as differences between fluorine concentration in tissues of exposed and control rats) are plotted against the time elapsed (in hours) from the end of the exposure until the sacrifice time. Each point represents differences of means of six exposed and six control rats: squares, liver; diamonds, kidney; circles, lung; triangles, muscle.

### *Skeletal Fluoride*

Fluoride concentrations in bones of unexposed rats were 12.4 ± 0.4 μmol fluorine/g dry bone. Fluoride concentrations in bones of any exposed rats were not significantly different from unexposed rats. This study shows that amounts of fluoride released by isoflurane or halothane metabolism are negligible and that the nonvolatile fluorine measured in tissues of exposed rats is mainly in nonionic form.

## Discussion

In an earlier study, isoflurane was shown to inhibit the oxidative metabolism of halothane (4). The results of the current study using female Sprague–Dawley rats indicate that oxidative metabolism of halothane is inhibited by 80% during anesthesia produced by 0.6% isoflurane, and that this inhibitory effect vanishes rapidly after the end of anesthesia. The oxidative metabolism of halothane was inhibited by 15% when halothane was administered 0.5 hr after the end of isoflurane anesthesia. No inhibition in oxidative metabolism was seen when halothane administration was further delayed. This transient reversible inhibition is unrelated to the presence of fluoride and trifluoroacetic acid in the body because urinary excretion of these metabolites has a half-time of approximately 20 hr (10,11), which is incompatible with the rapid restoration of halothane oxidative metabolism after isoflurane anesthesia. It appears, then, that the inhibition of halothane oxidative metabolism is related either to a metabolite other than trifluoroacetic acid and fluoride or to the presence of isoflurane itself.

The presence of another isoflurane metabolite is indicated in this study by the tissue distribution and biphasic elimination of nonvolatile fluorine (Fig. 1). The accumulation of nonvolatile fluorine in liver and its rapid elimination immediately after anesthesia are incompatible with the kinetics of any metabolite identified so far (12) and suggest the presence of a stable metabolite with a short elimination half-time. The rapid elimination of this unidentified metabolite is compatible with the rapid restoration of halothane metabolism after isoflurane anesthesia. Fluorine concentrations present in tissues 2.5 hr after the end of isoflurane anesthesia and thereafter were slightly elevated compared to tissues of unexposed rats and did not appear to decline. Such behavior is incompatible with the elimination of trifluoroacetic acid as seen in the halothane exposures (Fig. 1) and suggests the presence of fluorine-containing intermediates bound to tissue constituents. This conclusion is supported by Bradshaw and Ivanetich (12), who suggest that after the split of the ether linkage in isoflurane, the $CF_3$-CO-moiety is bound to cellular constituents. Further support comes from balance studies of isoflurane anesthesia in humans, which indicate that covalent binding may account for up to 5% of an anesthetic dose (11).

The inhibition of oxidative metabolism of halothane could be related to levels of isoflurane in the body. The rapid restoration of halothane oxidative metabolism after the end of isoflurane anesthesia is compatible with the rapid pulmonary clearance of isoflurane after anesthesia (10,11). In the current study, 2.5 hr after the end of isoflurane anesthesia, hepatic levels of isoflurane were 2% of levels reached at the end of anesthesia. Six hours after the end of anesthesia, levels of isoflurane were less than 0.5% of those measured during anesthesia. The presence of the perfluorinated carbon in isoflurane molecule prompts further speculation on mechanisms of inhibition of oxidative halothane metabolism by isoflurane. It has been shown that perfluorinated hydrocarbons are pseudosubstrates that resist the attack of the activated oxygen complex of cytochrome P-450 yet continue to stimulate NADPH oxidation in liver microsomes in a manner similar to other substrates (13,14), including enflurane and methoxyflurane (15). This results in uncoupling of the electron flow of the microsomal monoxygenase reaction and prevents oxidation of other drugs. If isoflurane acts as a pseudosubstrate, binding to the same site of cytochrome P-450 as halothane, then inhibition of oxidative metabolism would be competitive. The competitive inhibition is, however, inconsistent with the fact that the reductive metabolism of halothane, which is also mediated by cytochrome P-450, is unaffected by isoflurane. Thus the data support the theory of the existence of a genetically determined cytochrome P-450-isoenzyme variant that mediates the reductive metabolism of halothane (16,17) but has no affinity to isoflurane.

This study in rats confirmed transient inhibition of oxidative metabolism of halothane caused either by isoflurane or by its unknown metabolite with short elimination half-time. If inhibition is mediated by metabolism, isoflurane may not be an inhibitor in humans, because species differences in isoflurane metabolism were indicated (10,12). Until the mechanisms of the inhibitory effect of isoflurane and of hepatotoxicity of halothane are understood, switching between halothane and isoflurane during clinical anesthesia may not be advisable.

As a result of inhibition of oxidative metabolism mediated by microsomal mixed-function oxidase, elimination half-life of some drugs may be prolonged during isoflurane anesthesia, and consequently the therapeutic effect can be altered. Thus it is anticipated that sleeping time resulting from barbiturate administration is prolonged, as well as the activity of some hypoglycemic and anticoagulant drugs. Similar prolongation of elimination half-time is likely to be experienced during anesthesia with other potent inhalation anesthetics that competitively inhibit metabolism of other drugs (5). Such interaction of inhalation anesthetics with other drugs probably has very little clinical significance, because anesthesia is usually a short-lived episode, and because the activity of microsomal mixed-function oxidase is rapidly restored. The interaction of isoflurane with oxidative metabolism of drugs should be considered, however, if the drug is administered by infusion or if any drug administered during perianesthesia period has provoked an atypical reaction.

The technical assistance of Dahlia Williams, BS, Paul Lindeman, BS, and Frances Gil is gratefully acknowledged.

## References

1. Ikeda M. Reciprocal metabolic inhibition of toluene and trichloroethylene in vivo and in vitro. Int Arch Arbeitsmed 1974;33:125–30.
2. Wallen M, Naslund PH, Byfalt Nordqvist M. The effects of ethanol on the kinetics of toluene in man. Toxicol Appl Pharmacol 1984;76:414–20.
3. Fiserova-Bergerova V. Modeling of uptake and clearance of inhaled vapors and gases. In: Gut J, Cikrt M, Plaa GL, eds. Industrial and environmental xenobiotics. Berlin-Heidelberg-New York: Springer–Verlag, 1981:211–20.
4. Fiserova-Bergerova V. Inhibitory effect of isoflurane upon oxidative metabolism of halothane. Anesth Analg 1984;63:399–404.
5. Fish KJ, Rice SA. Halothane inhibits metabolism of enflurane in Fischer 344 rats. Anesthesiology 1983;59:417–20.
6. Widger LA, Gandolfi AJ, Van Dyke RA. Hypoxia and halothane metabolism in vivo: release of inorganic fluoride and halothane metabolite binding to cellular constituents. Anesthesiology 1976;44:197–201.
7. Maiorino RM, Sipes IG, Gandolfi AJ, Brown BR Jr, Lind BS. Factors affecting the formation of chlorotrifluoroethane and chlorodifluoroethylene from halothane. Anesthesiology 1981; 54:383–9.
8. Fiserova-Bergerova V, Kawiecki RW. Effects of exposure concentrations on distribution of halothane metabolites in the body. Drug Metab Dispos 1984;12:98–105.
9. Fiserova-Bergerova V. Changes of fluoride content in bone: an index of drug defluorination in vivo. Anesthesiology 1973; 38:345–51.
10. Hitt BA, Mazze RI, Cousins MJ, Edmunds HN, Barr GA, Trudell JR. Metabolism of isoflurane in Fischer 344 rats and man. Anesthesiology 1974;40:62–7.
11. Holaday DA, Fiserova-Bergerova V, Latto IP, Zumbiel MA. Resistance of isoflurane to biotransformation in man. Anesthesiology 1975;43:325–32.
12. Bradshaw JJ, Ivanetich KM. Isoflurane: a comparison of its metabolism by human and rat hepatic cytochrome P-450. Anesth Analg 1984;63:805–13.
13. Staudt H, Lichtenberger F, Ullrich V. The role of NADH in uncoupled microsomal monoxygenations. Eur J Biochem 1974;46:99–106.
14. Kutham H, Ullrich V. Oxidase and oxygenase function of the microsomal cytochrome P-450 monooxygenase system. Eur J Biochem 1982;126:583–8.
15. Ivanetich KM, Manca V, Harrison GG, Berman M. Enflurane and methoxyflurane: their interaction with hepatic microsomal stearate desaturase. Biochem Pharmacol 1980;29:27–34.
16. Brown BR Jr, McLain GE. The role of the liver. In: Smith NT, Miller RD, Corbascio AN, eds. Drug interactions in anesthesia. Philadelphia: Lea and Febiger, 1981;31–8.
17. Brown BR Jr, Sipes IG, Baker RK. Halothane hepatotoxicity and the reduced derivative, 1,1,1-trifluoro-2-chloroethane. Environ Health Perspect 1977;21:185–8.

# Disuse and *d*-Tubocurarine Sensitivity in Isolated Muscles

Barbara E. Waud, MD, Yoshikiyo Amaki, MD, and Douglas R. Waud, MD, DPhil

WAUD BE, AMAKI Y, WAUD DR. Disuse and *d*-tubocurarine sensitivity in isolated muscles. Anesth Analg 1985;64:1178–82.

*The effect of immobilization on subsequent sensitivity of limb muscles to d-tubocurarine was examined in a guinea pig model. A foreleg was immobilized in a cast for 1–4 weeks. At the end of this period, isolated nerve-lumbrical muscle preparations were set up and sensitivity to d-tubocurarine assayed. Immobilization increased the* $ED_{50}$ *of the drug not only in muscles from the limb in the cast but also those from contralateral forelimbs and from hindlimbs. The increase in* $ED_{50}$ *was not accompanied by atrophy. In a parallel series of experiments measuring the effect of d-tubocurarine on depolarization by carbachol, the apparent d-tubocurarine-receptor dissociation constant was determined. Immobilization produced no change in this parameter. Because immobilization of one extremity produced sensitivity changes in others, the anesthesiologist must be careful not to assume that monitoring from any limb will yield normal values in a patient with partial immobility.*

Key Words: NEUROMUSCULAR RELAXANTS—*d*-tubocurarine.

Resistance to the effects of nondepolarizing muscle relaxants has been demonstrated both in patients whose conditions may predispose to disuse atrophy (1,2) and in dogs whose hindlimbs have been immobilized in plaster casts (3). Although muscle disuse is associated with both receptor spread (4) and sprouting of the nerve terminal (5), it is not clear that these local changes are the basis of the decreased effect of muscle relaxants, or whether extraneous factors such as muscle blood flow play a role. The present study examined in vitro the effect of *d*-tubocurarine on muscles that had been immobilized to determine directly whether the resistance seen in vivo was a feature of the nerve–muscle system itself.

## Methods

The experiments were performed on isolated nerve–lumbrical muscle preparations obtained from guinea pigs after a period of forelimb immobilization in a plaster cast. The forelimb (side chosen at random) was fixed in a plaster cast from above the elbow to the tips of the digits. Care was taken to ensure that the distal opening did not permit appreciable movement of the digits because the intent was to immobilize the lumbrical muscles. When the immobilization was to be for more than a week, the cast was lined with a thin layer of padding to minimize the likelihood that growth could lead to too tight a fit and it was changed at about two weeks when the immobilization was to be three or four weeks. A collar of cardboard about 10 cm in diameter was mounted around the animal's neck. This collar prevented access to the cast but still allowed the animal to move freely about the cage, to eat, and to drink. Controls with a collar only or with neither collar nor cast were included.

To offset the effect of growth on the size of the pig and muscle at the time of assay, the longer periods of immobilization were started in younger animals. This was successful inasmuch as an analysis of variance at the end of the study showed no significant variation among weight of animals at the time of assay (390 ± 63 g, mean ± SD). The weight gains were about 25 g/week.

At the end of the period of immobilization the lumbrical muscle and its associated nerve were removed from the limb in the cast along with a muscle from the contralateral control forelimb and from one hindlimb of unselected side (occasionally one of these controls was lost because of the difficulty in dissecting the preparation).

The preparation was mounted in an isolated organ bath for isometric tension recording at the resting tension yielding maximal developed tension. The nerve was mounted in a tunnel electrode and stimulated every 10 sec with a shock lasting 0.1 msec at twice the intensity producing a maximal twitch response.

---

Received from the Departments of Anesthesiology and Pharmacology, University of Massachusetts Medical Center, Worcester, Massachusetts. Accepted for publication June 14, 1985.

Address correspondence to Dr. B.E. Waud, Department of Anesthesiology, University of Massachusetts Medical Center, Worcester, MA 01605.

© 1985 by the International Anesthesia Research Society

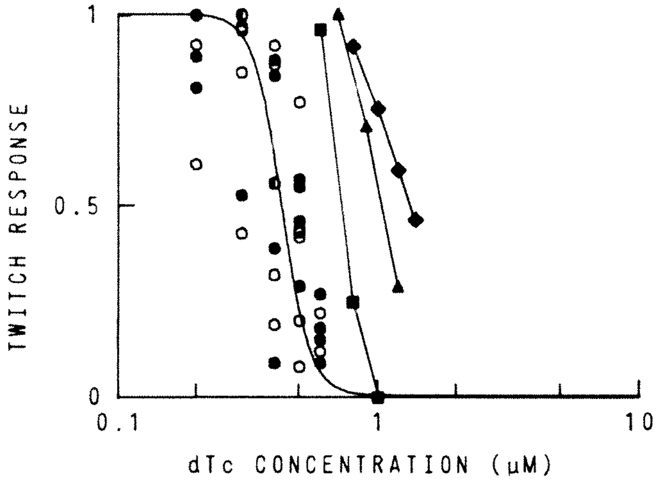


Figure 1. Example of response to *d*-tubocurarine in muscles from control and immobilized limbs. *Ordinates:* fractional twitch responses to nerve stimulation. *Abscissae:* concentrations of tubocurarine. *Full circles:* control values from the forelimbs of animals with no restraint. *Open circles:* same from hindlimbs. Twelve preparations are represented. In each, a logistic function ($Tw = 1 - [dTc]^S/([dTc]^S + ED_{50}^S)$; where $S$ is determined by the steepness of the relationship) was fitted to the observations. The mean values of the parameters $ED_{50}$ and $S$ were used to draw the sigmoid curve. *Diamonds:* corresponding values for a forelimb that has been in a cast for one week. *Triangles:* contralateral control from the animal in the cast. *Squares:* hindlimb control from that animal.

The bathing solution was of the following composition (mM): $Na^+$ 138; $K^+$ 5.9; $Cl^-$ 118; $Ca^{2+}$ 1.26; $Mg^{2+}$ 1.2; $H_2PO_4^-$ 1.2; $SO_4^{2-}$ 1.2; $HCO_3^-$ 25; lactate 2.5; plus 2.08 g/L glucose bubbled with 95% $O_2$–5% $CO_2$ and kept at 37°C. The drug dilutions were made in a separate chamber at 37°C, and then the final solution was added by overflow (6). The dose–response curve to *d*-tubocurarine was determined by adding the drug in stepwise concentrations selected to span levels of block between none and full. The preparation was equilibrated in the bath for 20–30 min before the assay began, and the drug was left in contact with the preparation until the twitch stabilized at each dose level.

In a parallel set of studies the isolated muscle was mounted (without the nerve) in the same bathing solution but in an apparatus for recording depolarization of the end-plate region extracellularly by the moving fluid electrode technique (7). In these muscles the apparent *d*-tubocurarine–receptor dissociation constant was determined by the conventional dose–ratio technique (8).

At the end of the procedure, muscles were fixed at their resting length and subsequently embedded in paraffin, sectioned serially, and stained. The largest cross section was projected onto a video monitor and the area of the muscle measured as an estimate of muscle size (area was approximated by assuming an elliptical shape and taking ($\pi/4$) times the product of the major and minor axes). The control maximal developed tension was used as a second indicator of size. Both values were normalized by dividing by the animal's weight taken to the ⅔ power (to scale roughly from volume to area). Effects demonstrable at the 95% probability level were considered significant.

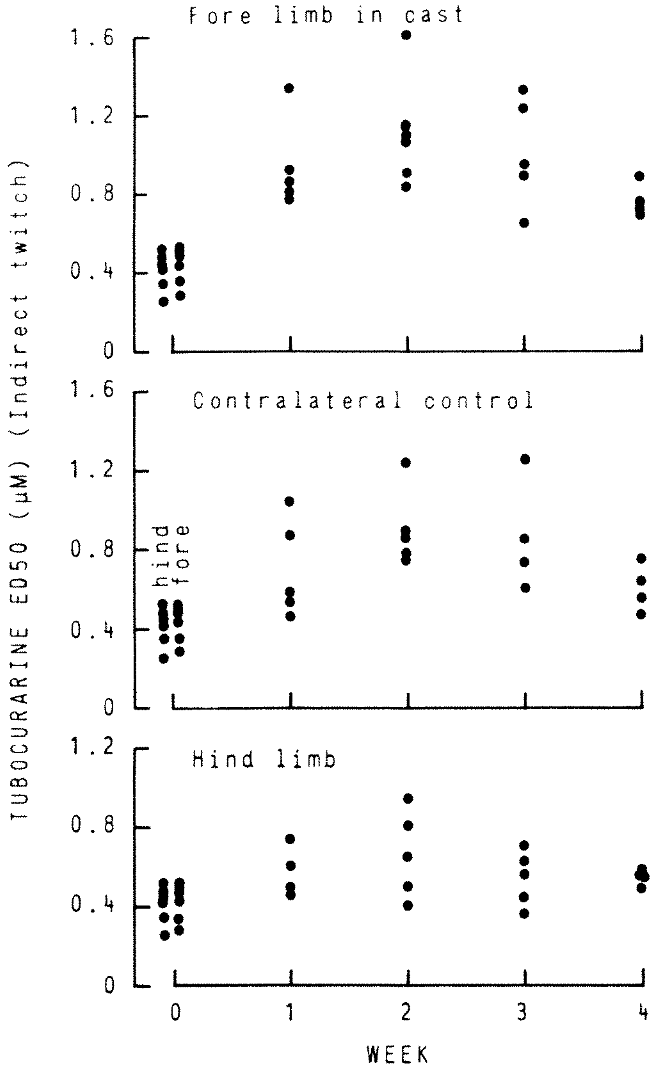


Figure 2. Summary of the effect of immobilization on sensitivity to *d*-tubocurarine. *Ordinates:* $ED_{50}$ values for *d*-tubocurarine in blocking the indirect twitch response. *Abscissae:* durations of immobilization of a forelimb in a cast. *Upper panel:* muscles from immobilized forelimbs. *Middle panel:* muscles from contralateral forelimbs. *Lower panel:* muscles from hindlimb. Values at time zero are the same in all panels; fore- and hindlimb controls, though indistinguishable, are plotted with the latter values shifted to the left of the former.

## Results

The general nature of the results is illustrated easily in Figure 1, which presents dose–response curves in three test muscles from an animal chosen because it demonstrated a marked effect. For reference, the cir-

Table 1. *d*-Tubocurarine $ED_{50}$ ($\mu M$)

| | Weeks immobilized | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 |
| Control | 0.429 ± 0.026<br>(12) | | | | |
| Forelimb in cast | | 0.945 ± 0.103<br>(5) | 1.115 ± 0.110<br>(6) | 1.012 ± 0.122<br>(5) | 0.761 ± 0.041<br>(4) |
| Contralateral forelimb | | 0.705 ± 0.109<br>(5) | 0.907 ± 0.089<br>(5) | 0.865 ± 0.138<br>(4) | 0.606 ± 0.061<br>(4) |
| Hindlimb | | 0.571 ± 0.067<br>(4) | 0.663 ± 0.100<br>(5) | 0.547 ± 0.059<br>(5) | 0.547 ± 0.018<br>(4) |
| | | Weeks in collar | | | |
| | | 1 | 2 | 3 | 4 |
| Forelimb | | 0.546 ± 0.068<br>(5) | 0.504 ± 0.048<br>(5) | 0.622 ± 0.086<br>(5) | 0.490 ± 0.031<br>(5) |
| Hindlimb | | 0.522 ± 0.024<br>(5) | 0.542 ± 0.027<br>(5) | 0.485 ± 0.029<br>(5) | 0.455 ± 0.021<br>(5) |

Values given as mean ± SEM. *n* in parenthesis.

cles and curve give values from 12 limb muscles from normal unrestrained guinea pigs. The values for a forelimb that has been in a cast for a week (diamonds) fall far to the right; the $ED_{50}$, 1.33 $\mu M$, is about fourfold higher than that, 0.43 $\mu M$, of the control group. Interestingly, the values for the other two muscles from the animal in the cast also show an increased resistance to the drug. The muscle from the hindlimb (squares) is not shifted so much as that from the contralateral forelimb (triangles).

The results from many such experiments and over a wider range of durations of immobilization are summarized in Figure 2 and Table 1. First there is clearly a considerable amount of scatter. This is not surprising; the degree of immobilization is hard to standardize closely because the extent of padding (both hair and extrinsic) is not easily controlled, and the animals wiggle to varying degrees while the cast is applied. Nevertheless, there can be a very marked effect of immobilization. And, as suggested in Figure 1, the resistance to *d*-tubocurarine is significant not only in the limb in a cast but in other extremities as well.

The results in Figure 2 can be examined more closely. First, we did a one-way analysis of variance comparing the five sets of values at 0, 1, 2, 3, and 4 weeks. The result was a large and very significant *F* ratio (17.53; 4, 27 *df*; $P < 0.001$). Next, inspection of the figure indicates a large contribution probably came in the first week. Possibly there was a slight fall-off by the fourth week. We tested this by repeating the analysis of variance with the values for week zero removed. Now the value of *F* decreased to 1.86 (3, 16 *df*), an insignificant level. Thus the results suggest the change we see occurs by the end of the first week of immobilization and changes negligibly thereafter. The values in the middle panel of Figure 2 behaved similarly (*F* values of 9.22 and 1.81). Those in the bottom panel showed only a marginal difference; the *F* ratio (3.27; 3, 25 *df*) was significant at only the 0.05 level.

Because these results suggest that the effect of the cast was not restricted to the immobilized limb, a series of control animals with the restraining collar but no cast was examined. The results are summarized in Figure 3 and Table 1. Analysis of variance indicates there was no significant difference among times; the collar was without effect.

The next question examined was whether the resistance to the drug resulted from a change in the chemical reactivity of the receptor. Figure 4 shows the results. There is no sign that the properties of the receptor change with immobilization.

To see whether the resistance to the drug reflected some effect of disuse atrophy, the size of the muscle was monitored, both directly as cross-sectional area and indirectly as the peak developed tension, for comparison with the results in Figure 2. Figure 5 summarizes the findings. The degree of immobilization produced by the cast did not lead to a detectable change in size of the muscle; analysis of variance of the values in Figure 5 yielded no significant differences.

## Discussion

Our results parallel those found in patients (1,2) and dogs (3). Thus the behavior found in vivo does not reflect a circulatory or pharmacokinetic artifact but rather some change in the neuromuscular apparatus

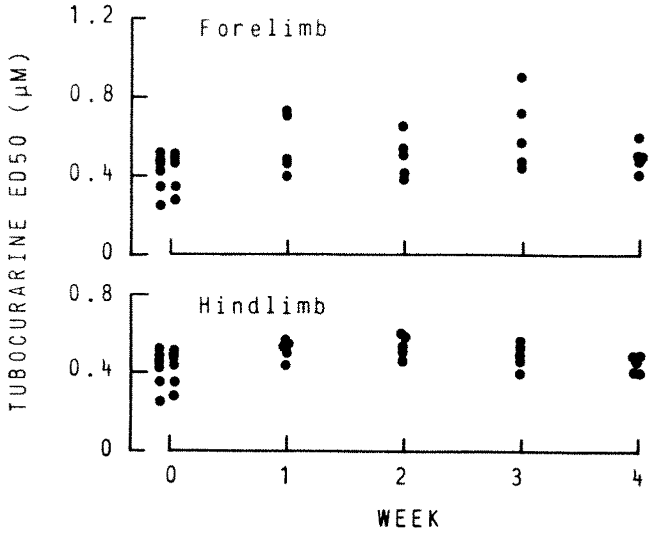


Figure 3. Effect of restraining collar. Plot as in Figure 2.

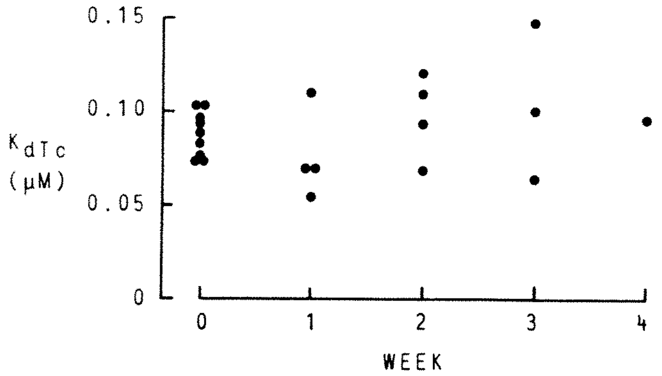


Figure 4. Effect of immobilization on the *d*-tubocurarine–receptor dissociation constant. Plot format as in Figure 2 except that the ordinates are values of the dissociation constant. Control values are from pooled fore- and hindlimbs. At one to four weeks values for only the immobilized limb are shown.

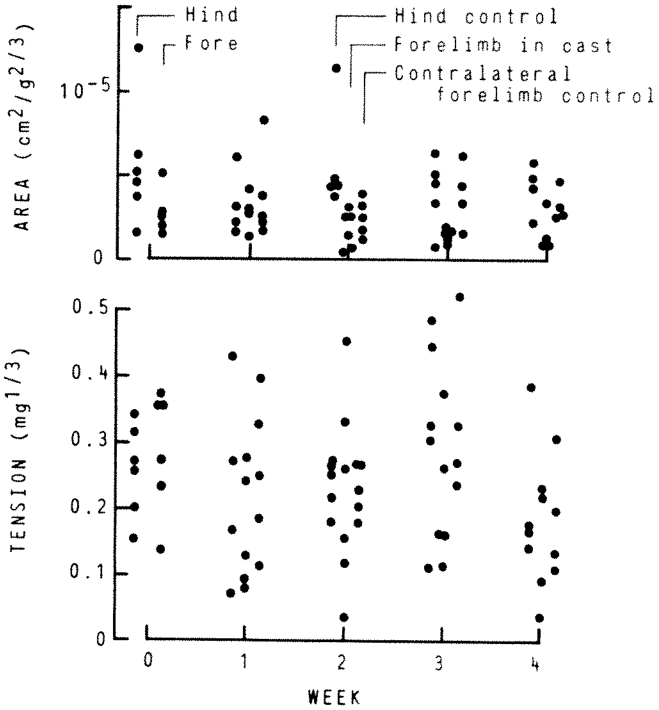


Figure 5. Effect of immobilization on muscle size. Format as in Figure 2 except that ordinates are muscle areas in the upper panel and peak developed tensions in the lower panel. In both cases the values have been normalized for size of animal by dividing by body weight raised to the ⅔ power.

itself. The absence of change in the *d*-tubocurarine receptor dissociation constant suggests the receptors themselves have not changed. The absence of concomitant atrophy implies a mechanism distinct from simple change in size of the muscle. Our experiments do not allow us to decide whether or not nerve terminal sprouting (5) or spread of receptors (4) is involved (although the latter phenomenon, if present at all, was not of sufficient magnitude for us to notice a change in the spatial distribution of the depolarization recorded in our moving fluid electrode experiments; this is not a very sensitive test because most of the spread presumably represents electrotonic factors, not distribution of receptors).

The measures of muscle size used to monitor atrophy—peak developed tension and maximal cross-sectional area—deserve comment. Atrophy should reduce the cross-sectional area of cells and also the force that cells can develop. However, we still observed considerable variation. Therefore, because it is reasonable to expect that larger pigs would have larger muscles, we tried to eliminate this factor by normalizing on the basis of weight. Because weight goes up with volume, i.e., as the cube of length, and area as the square of length, we have converted weight to the dimensions of area by taking its two-thirds power. While rational, this maneuver was still unable to reduce the scatter enough for us to detect any sign of atrophy. Apparently, the lumbrical muscle suffers from the disadvantage of being particularly variable in size.

Inspection of individual points in Figure 5 does suggest there may be some signs of atrophy hidden in the noise. In particular, the measurements of area of the limb in a cast at three and four weeks show a preponderance of low values. It is not practical to get a sample size large enough to confirm this impression of a trend. In any case, even if muscle size is beginning to drop by the third or fourth week, this time course would differ from that for the increase in sensitivity seen in Figure 2. The latter effect appears earlier.

The extent of involvement of muscles from limbs not in a cast was surprising. Our experiments do not allow us to say why. We suspect the presence of a cast on one foot leads to reduced activity in toto and this surfaces as a decrease in sensitivity to *d*-tubocurarine.

Whereas analysis of variance indicated no significant differences among the temporal groups in those animals with restraining collar but not cast, inspection of the values at one, two, and three weeks shows a few values above the range of the control (week zero) values. Possibly even such a slight impediment to motility as was presented by the collar can lead to a shift of sensitivity. This, of course, is in line with our impression that the changes seen in the muscles from control limbs of immobilized animals reflect a generalized effect of interference with mobility. The effect can be pronounced in a given individual. For example see Figure 3; at three weeks one of the animals had an $ED_{50}$ of 0.9 $\mu$M, double the control mean. That would correspond to a dosage requirement of 60 mg instead of 30 mg in a patient.

Regardless of the cause, the generalized effect of local immobilization is important. It implies that the anesthesiologist using a peripheral nerve stimulator in the operating room should not assume that placement of the apparatus on a limb other than that where immobilization or disuse atrophy is present will be associated with a "normal" recording. For example, if a neuromuscular blocking agent is titrated against that limb, if that limb is exhibiting the reduced sensitivity we describe, and if the diaphragm does not, then paralysis of respiration may be more severe than intended or appreciated.

## References

1. Graham DH. Monitoring neuromuscular block may be unreliable in patients with upper-motor-neuron lesions. Anesthesiology 1980;52:74–5.
2. Martyn JAJ, Szyfelbein SK, Ali HH, et al. Increased *d*-tubocurarine requirement following major thermal injury. Anesthesiology 1980;52:352–5.
3. Gronert GA. Disuse atrophy with resistance to pancuronium. Anesthesiology 1981;55:547–9.
4. Fischbach GD, Robbins N. Effect of chronic disuse of rat soleus neuromuscular junction on postsynaptic membrane. J Neurophysiol 1971;34:562–9.
5. Snider WD, Harris GL. A physiological correlate of disuse-induced sprouting at the neuromuscular junction. Nature 1979;281:69–71.
6. Waud DR, Waud BE. A simple easily-constructed isolated organ bath for nerve-muscle studies. Pharmacologist 1981;23:130.
7. Fatt P. The electromotive action of acetylcholine at the motor end-plate. J Physiol 1950;111:408–22.
8. Lee Son S, Waud BE. Potencies of neuromuscular blocking agents at the receptor of the atrial pacemaker and the motor endplate of the guinea pig. Anesthesiology 1977;47:34–6.

ANESTH ANALG 1985;64:1183–8

# Effects of Volatile Anesthetics or Fentanyl on Hepatic Function in Cirrhotic Rats

Jeffrey M. Baden, MD, Yashdev R. Kundomal, PhD, Michael E. Luttropp Jr, BS, Mervyn Maze, MD, and Jon C. Kosek, MD

BADEN JM, KUNDOMAL YR, LUTTROPP ME, MAZE M, KOSEK JC. Effects of volatile anesthetics or fentanyl on hepatic function in cirrhotic rats. Anesth Analg 1985;64:1183–8.

*Halothane, enflurane, isoflurane, and fentanyl were examined for their potential to exacerbate liver dysfunction in rats with preexisting cirrhosis. Male Wistar rats given sodium phenobarbital for 2 weeks are assigned randomly to two groups. One group (cirrhotic) was exposed by inhalation to carbon tetrachloride ($CCl_4$) in air at weekly intervals for 12 weeks to induce cirrhosis. The other group (noncirrhotic) was handled similarly but received air only. Five weeks after the last exposure to $CCl_4$, cirrhotic and noncirrhotic rats were given three hours of 1 MAC halothane, enflurane, or isoflurane in 50% oxygen, or 350 μg fentanyl per kg of body weight and 50% oxygen, or 50% oxygen only. Blood gas tensions and blood glucose levels were measured before, during, and at the end of exposure. Forty-eight hours after exposure, serum chemistries were measured in each rat for comparison with preexposure values. Rats were then killed by $CO_2$ overdose, and liver, kidney, and testis were prepared for microscopic examination. Enflurane, isoflurane, and halothane, but not fentanyl, produced mild respiratory acidosis and no change in serum glucose levels. All anesthetics resulted in a mild but similar degree of acute liver dysfunction as indicated by small increases in SGOT or SGPT in both cirrhotic and noncirrhotic rats. Liver histology revealed mild to moderate portal cirrhosis with fibrosis and well-developed micronodules in rats exposed to $CCl_4$, but no superimposed acute hepatocellular damage was noted. It is concluded that all the anesthetics used in this study were associated with the same minimal degree of postanesthetic hepatic dysfunction and that the dysfunction was similar in both cirrhotic and noncirrhotic rats.*

Key Words: ANESTHETICS, VOLATILE—enflurane, halothane, isoflurane. ANALGESICS—fentanyl. LIVER—cirrhosis.

The number of individuals with liver disease has increased steadily over the last 40 years in the United States, due mainly to the increase in alcohol abuse (1,2). Even greater increases have been seen in Canada where cirrhosis is now one of the leading causes of death for men in the productive years from 25 to 64 (3). More cirrhotic patients are, therefore, presenting for anesthesia and surgery, and an even greater number may be expected in the future. Limited evidence indicates that liver function in cirrhotic patients is made worse by surgery, whether performed under general (with either cyclopropane or ether) or regional anesthesia (4). However, modern anesthetic drugs and techniques have not been investigated adequately. Thus we undertook to determine whether the currently used inhalation anesthetics, halothane, enflurane, and isoflurane, and the narcotic analgesic, fentanyl, exacerbate liver dysfunction in experimental animals with normal livers and preexisting liver cirrhosis. We used a model of cirrhosis in the rat that we have recently refined in our laboratory (5).

## Materials and Methods

Two hundred male Wistar rats (Hilltop Labs, Chatsworth, CA), 200–230 g, were individually ear-tagged and randomly divided into two groups. They were housed four to a cage and were bedded on ground corn cob (Paxton Processing Company, Paxton, IL) in polypropylene plastic cages with stainless steel lids. They were supplied with small animal chow (Wayne Lab Blox, Allied Mills, Inc., Chicago, IL) and tap water at all times, except during treatment when both were removed. Rats were weighed twice weekly throughout the study. After a 2-week period of quarantine,

---

Supported in part by Anaquest, the Veterans Administration and the Department of Anesthesia, Stanford University School of Medicine.

Received from the Departments of Anesthesia and Pathology, Stanford University School of Medicine (SUSM), Stanford, California and Anesthesiology and Pathology Services, Veterans Administration Medical Center (VAMC), Palo Alto, California. Accepted for publication June 24, 1985.

Address correspondence to Dr. Baden, Anesthesiology Service (112A), VA Medical Center, Palo Alto, CA 94304.

© 1985 by the International Anesthesia Research Society

Table 1. Body Weights (g, mean ± SEM)

| Group | Before $CCl_4$ | After $CCl_4$ | Before anesthesia and analgesia |
|---|---|---|---|
| Noncirrhotic rats ($n$ = 60) | 215 ± 2.0 | 431 ± 4.0 | 450 ± 4.3 |
| Cirrhotic rats ($n$ = 55) | 223 ± 2.1 | 400 ± 4.0[a] | 417 ± 5.8[a] |

[a] Significantly less than noncirrhotic rats ($P < 0.05$).

0.05% sodium phenobarbital was added to the drinking water. One week later, one group of rats (cirrhotic) was exposed for 2 min to 1–2% carbon tetrachloride ($CCl_4$) in air in a 100-L Plexiglas chamber. Each week thereafter each rat was exposed to $CCl_4$ for progressively longer times, reaching a maximum of 8 min by the final exposure in the twelfth week. Concentrations of $CCl_4$ were measured several times during each exposure with a Hewlett Packard model 5820A gas chromatograph. After the last $CCl_4$ exposure, sodium phenobarbital was discontinued. The other group of rats (noncirrhotic) was handled similarly but were exposed to air only. Three weeks after the last exposure to $CCl_4$, an SMAC 20 was performed using a Technicon autoanalyzer on serum obtained from tail-blood of each rat. The albumin/globulin (A/G) ratios, the serum bilirubin levels, and the weight data indicated that all 80 surviving rats exposed to $CCl_4$, but none exposed to air, had developed some degree of cirrhosis. Fifteen cirrhotic rats were assigned to each of five groups so that the degree of cirrhosis was about the same in each group. In addition, sixteen noncirrhotic rats were assigned randomly to each group. Two weeks after the first SMAC 20, a second SMAC 20 was taken. Twenty-four hours later, four cirrhotic and four noncirrhotic rats from each group were chosen randomly, and their right carotid arteries were cannulated under ketamine anesthesia (70 mg/kg of body weight). Twenty-four hours later, groups were treated with one of the following: 1.44% (1 MAC) isoflurane in 50% oxygen (group 1); 1.05% (1 MAC) halothane in 50% oxygen (group 2); 2.20% (1 MAC) enflurane in 50% oxygen (group 3); one subcutaneous injection of 350 μg fentanyl per kg of body weight and 50% oxygen (group 4); and 50% oxygen (group 5). Arterial blood for measurement of gas tensions and glucose levels was obtained from cannulated rats immediately prior to anesthesia or exposure to 50% oxygen. All exposures were for 3 hr in a 1000-L capacity Plexiglas chamber. During exposure, anesthetic concentrations were monitored continuously with a Miran 1-F infrared gas analyzer and were kept within 5% of the desired value. Oxygen concentration was monitored continuously with an IL-402 oxygen monitor and maintained between 48 and 52%. Carbon dioxide concentration was intermittently monitored with a Beckman LB-2 analyzer and was kept less than 0.1%. Chamber temperature was monitored continuously and kept at a level that maintained the rats' body temperature between 36 and 38°C. Blood pressure was monitored intermittently during exposure, and blood samples were taken at 1.5 and 3 hr for measurements of blood gas tensions and glucose levels. Forty-eight hours after treatment, rats were again tail-bled for a SMAC 20, then killed by carbon dioxide overdose, and autopsied. Tissues were examined in situ, then dissected from the carcass and reexamined. Liver, kidneys, spleen, and testes were weighed fresh and fixed in 10% neutral buffered formalin. Histologic sections (4–6 μm thick) were cut from all five lobes of the liver of each rat and were stained with hematoxylin and eosin or with Mallory's trichrome for collagen. Histologic features of cirrhosis and superimposed acute hepatocellular damage were assessed without knowledge of treatment. These were graded as absent, mild, moderate, or severe, based on accepted histologic criteria (6). In addition, testis and kidney sections from selected cirrhotic and noncirrhotic rats were prepared and examined for damage. Analysis of variance and Student's *t*-test were used to determine differences among the groups; $P < 0.05$ was considered statistically significant.

## Results

Twenty percent of rats exposed to $CCl_4$ over a 12-week period died, whereas none of the rats exposed only to air died. Most deaths occurred after one or two exposures to $CCl_4$ and were due to acute liver damage. Later deaths were due to the complications of chronic liver failure such as infection and pleural effusions leading to respiratory failure. Thus the surviving cirrhotic rats were those most resistant to the effects of $CCl_4$.

Mean body weight in the cirrhotic group was significantly lower than in the noncirrhotic group after the first exposure to $CCl_4$ and remained lower throughout the study (Table 1). The A/G ratio was

Table 2. Selected Serum Chemistries (mean ± SEM)

| Group | After $CCl_4$ A/G ratio | After $CCl_4$ SGOT[a] | After $CCl_4$ SGPT[a] | Before anesthesia and analgesia A/G ratio | Before anesthesia and analgesia SGOT[a] | Before anesthesia and analgesia SGPT[a] |
|---|---|---|---|---|---|---|
| Noncirrhotic rats ($n$ = 60) | 1.18 ± 0.02 | 88 ± 2.0 | 60 ± 2.0 | 1.18 ± 0.01 | 108 ± 13.1 | 77 ± 8.7 |
| Cirrhotic rats ($n$ = 55) | 0.90 ± 0.01[b] | 208 ± 13.1[b] | 161 ± 6.6[b] | 0.96 ± 0.02[b] | 98 ± 8.0 | 82 ± 4.9 |

[a] In IU/L.

[b] Significantly different from noncirrhotic rats ($P < 0.01$).

Table 3. Selected Serum Chemistries (Mean ± SEM) Before and After Exposure to Anesthesia/Analgesia

| Group | SGOT[a] Before | SGOT[a] After | SGPT[a] Before | SGPT[a] After | A/G ratio Before | A/G ratio After |
|---|---|---|---|---|---|---|
| Noncirrhotic rats | | | | | | |
| Isoflurane ($n$ = 12) | 93.25 ± 5.36 | 111.92 ± 6.67[b] | 63.92 ± 4.47 | 67.00 ± 2.45 | 1.18 ± 0.01 | 1.24 ± 0.02 |
| Halothane ($n$ = 12) | 95.41 ± 5.67 | 95.00 ± 4.05 | 88.00 ± 4.24 | 87.42 ± 3.84 | 1.16 ± 0.02 | 1.19 ± 0.04 |
| Enflurane ($n$ = 11) | 99.17 ± 7.03 | 110.18 ± 4.13[c] | 68.83 ± 3.50 | 82.64 ± 4.65[c] | 1.14 ± 0.02 | 1.22 ± 0.03 |
| Fentanyl ($n$ = 12) | 89.00 ± 2.93 | 101.50 ± 4.35[c] | 63.10 ± 2.14 | 68.75 ± 2.04 | 1.19 ± 0.01 | 1.18 ± 0.01 |
| Oxygen ($n$ = 12) | 98.25 ± 8.67 | 106.08 ± 9.42 | 62.17 ± 11.85 | 72.17 ± 9.53 | 1.23 ± 0.02 | 1.19 ± 0.01 |
| Cirrhotic rats | | | | | | |
| Isoflurane ($n$ = 9) | 91.89 ± 4.40 | 92.11 ± 7.77 | 68.22 ± 4.11 | 80.33 ± 6.58[b] | 1.02 ± 0.05 | 1.02 ± 0.06 |
| Halothane ($n$ = 11) | 88.27 ± 3.78 | 96.82 ± 7.37 | 79.64 ± 5.79 | 110.64 ± 0.53[c] | 1.02 ± 0.02 | 1.08 ± 0.03 |
| Enflurane ($n$ = 11) | 102.00 ± 8.74 | 124.45 ± 11.67[c] | 88.73 ± 10.57 | 115.09 ± 14.04[c] | 1.00 ± 0.02 | 1.02 ± 0.02 |
| Fentanyl ($n$ = 11) | 85.08 ± 8.37 | 108.42 ± 10.56[b] | 75.17 ± 7.05 | 76.08 ± 5.04 | 0.92 ± 0.05 | 0.93 ± 0.04 |
| Oxygen ($n$ = 11) | 83.00 ± 8.19 | 89.45 ± 8.81 | 87.73 ± 7.76 | 95.09 ± 7.17 | 0.93 ± 0.02 | 0.95 ± 0.02 |

[a] In IU/L.

[b] $P < 0.05$ Pre vs post values.

[c] $P < 0.01$ Pre vs post values.

significantly lower in the cirrhotic group than in the noncirrhotic group 3 weeks after the last $CCl_4$ exposure and immediately before anesthesia and analgesia (Table 2). SGOT and SGPT levels, significantly higher in the cirrhotic group than in the noncirrhotic group 3 weeks after the last $CCl_4$ exposure, had returned to normal immediately before anesthesia and analgesia (Table 2).

Two cirrhotic rats died during exposure to isoflurane and one noncirrhotic rat died during exposure to enflurane. The cause of these deaths was not established, though the two cirrhotic rats had the greatest degree of cirrhosis in the isoflurane group. All other rats recovered quickly after the exposure to anesthesia and analgesia and appeared in excellent health.

SGOT and SGPT levels after anesthetic and analgesic exposure in both cirrhotic and noncirrhotic rats were generally increased compared with preanesthetic and analgesic values for all groups other than the oxygen-treated group (Table 3). These increases, though small in magnitude, were often statistically significant. Although there were minor differences, the overall effects of anesthesia and analgesia on SGOT and SGPT values were about the same in cirrhotic and noncirrhotic rats for all groups. Other serum chemistries, including alkaline phosphatase and total bilirubin, were not changed after exposure to anesthesia and analgesia.

Blood pressure and oxygenation remained normal throughout exposure to anesthesia and analgesia. In general, $Pa_{CO_2}$ in the anesthetic exposed groups increased slowly from about 35 to 55 mm Hg, and pH decreased from about 7.5 to 7.3 (Table 4), a pattern consistent with a respiratory acidosis. The effects of fentanyl on $Pa_{CO_2}$ and pH were much less marked.

No changes were seen in blood glucose levels in either cirrhotic or noncirrhotic rats during exposure to anesthesia and analgesia. The mean values for all the groups of cirrhotic and noncirrhotic rats were about 110 mg of glucose per dl of blood (range 90–140 mg), and they did not change significantly throughout the 3-hr treatment.

Mean liver and kidney weights of cirrhotic rats were slightly greater than those of noncirrhotic rats (Table 5). In addition, the mean spleen weights of cirrhotic rats were significantly greater ($P < 0.01$) than those of the noncirrhotic rats (Table 5). The mean weights of the testes in the cirrhotic rats were slightly less

Table 4. Blood Gas Tensions (Mean ± SEM) at the Start and Conclusion of Exposure to Anesthetics/Analgesia

| Group | $Pa_{O_2}$[a] Start | $Pa_{O_2}$[a] End | $Pa_{CO_2}$[a] Start | $Pa_{CO_2}$[a] End | pH Start | pH End |
|---|---|---|---|---|---|---|
| Noncirrhotic rats | | | | | | |
| Isoflurane (*n* = 2) | 85.50 ± 8.50 | 198.50 ± 2.50 | 38.50 ± 5.50 | 57.00 ± 10.00 | 7.48 ± 0.03 | 7.35 ± 0.55 |
| Halothane (*n* = 4) | 91.75 ± 1.38 | 186.67 ± 5.33 | 32.25 ± 1.58 | 55.67 ± 4.41 | 7.51 ± 0.02 | 7.35 ± 0.21 |
| Enflurane (*n* = 4) | 93.75 ± 0.95 | 195.75 ± 10.32 | 30.00 ± 0.41 | 59.25 ± 2.25 | 7.58 ± 0.01 | 7.30 ± 0.17 |
| Fentanyl (*n* = 3) | 88.33 ± 4.41 | 161.33 ± 25.09 | 32.00 ± 0.58 | 37.00 ± 2.08 | 7.52 ± 0.00 | 7.51 ± 0.17 |
| Oxygen (*n* = 2) | 85.50 ± 5.50 | 194.00 ± 5.00 | 33.50 ± 0.50 | 33.50 ± 1.50 | 7.50 ± 0.01 | 7.45 ± 0.50 |
| Cirrhotic rats | | | | | | |
| Isoflurane (*n* = 2) | 95.50 ± 6.50 | 165.50 ± 5.50 | 29.50 ± 4.50 | 61.00 ± 6.00 | 7.53 ± 0.02 | 7.31 ± 0.03 |
| Halothane (*n* = 3) | 83.33 ± 1.76 | 185.67 ± 7.31 | 31.67 ± 0.33 | 52.33 ± 3.18 | 7.48 ± 0.01 | 7.34 ± 0.02 |
| Enflurane (*n* = 4) | 95.00 ± 1.27 | 203.75 ± 6.17 | 30.25 ± 1.49 | 63.75 ± 5.50 | 7.50 ± 0.02 | 7.26 ± 0.04 |
| Fentanyl (*n* = 4) | 100.00 ± 5.48 | 125.00 ± 10.00 | 27.25 ± 1.55 | 35.50 ± 1.50 | 7.53 ± 0.02 | 7.46 ± 0.02 |
| Oxygen (*n* = 4) | 90.00 ± 4.16 | 195.00 ± 5.84 | 33.33 ± 2.40 | 26.67 ± 3.71 | 7.49 ± 0.01 | 7.57 ± 0.04 |

[a] Measured in mm Hg.

Table 5. Organ Weights (g, mean ± SEM)

| Group | Liver | Kidneys Right | Kidneys Left | Spleen | Testes Right | Testes Left |
|---|---|---|---|---|---|---|
| Noncirrhotic rats (*n* = 59) | 16.34 ± 4.06 | 1.62 ± 0.16 | 1.63 ± 0.16 | 0.79 ± 0.09 | 1.89 ± 0.16 | 1.88 ± 0.15 |
| Cirrhotic rats (*n* = 53) | 17.94 ± 2.99 | 1.68 ± 0.22 | 1.67 ± 0.22 | 1.03 ± 0.28[a] | 1.76 ± 0.15 | 1.75 ± 0.18 |

[a] Significantly greater than noncirrhotic group ($P < 0.01$).

than those of the noncirrhotic rats, although no testicular atrophy was observed on histologic examination.

Histologically, livers of rats exposed to $CCl_4$ showed mild to moderate portal cirrhosis with fibrosis and well-developed micronodules but only slight evidence of fatty infiltration. Neither livers of cirrhotic rats nor those of noncirrhotic rats showed evidence of acute necrosis. No significant histologic changes were observed in kidneys or testes.

## Discussion

Most clinicians believe that liver function in cirrhotic patients is made worse by anesthesia and surgery, yet little work has been done to determine the causes. In an early study, French et al. found that postoperative liver dysfunction is greater in patients with chronic liver disease, most notably cirrhosis, than in patients with normal preoperative liver function who were having similar operations (4). They also noted that although the separate contributions of surgery and anesthesia with diethyl ether or cyclopropane could not be determined, the extent to which liver function worsened was correlated closely with the severity of the preexisting liver disease. The possible reasons for such a correlation were not elucidated. Furthermore, this study was performed before the introduction of modern halogenated anesthetics, and a paucity of information exists on both the degree to which agents like halothane contribute to liver dysfunction in patients with chronic liver disease and on the mechanisms involved (5). It may seem surprising that little further work has been done in humans. There are, however, several reasons for this. First, the degree of functional impairment varies widely among patients diagnosed as having a specific type of chronic liver disease. Second, currently used clinical and laboratory criteria for assessing the severity of liver dysfunction are relatively crude; therefore, it is difficult to stratify study groups on the basis of severity of disease. Because groups are usually heterogeneous, statistical power is low unless large and often unattainable group sizes are used. The difficulty in assessing severity of liver disease also creates difficulties in assessing small to moderate changes in liver function after a particular treatment. Third, patients with chronic liver disease often receive concomitant therapy with a multitude of other drugs, raising the possibility of confounding drug–drug interactions. Finally, there remains the problem of dissociating the effects of anesthesia on postoperative liver function from the effects of surgery.

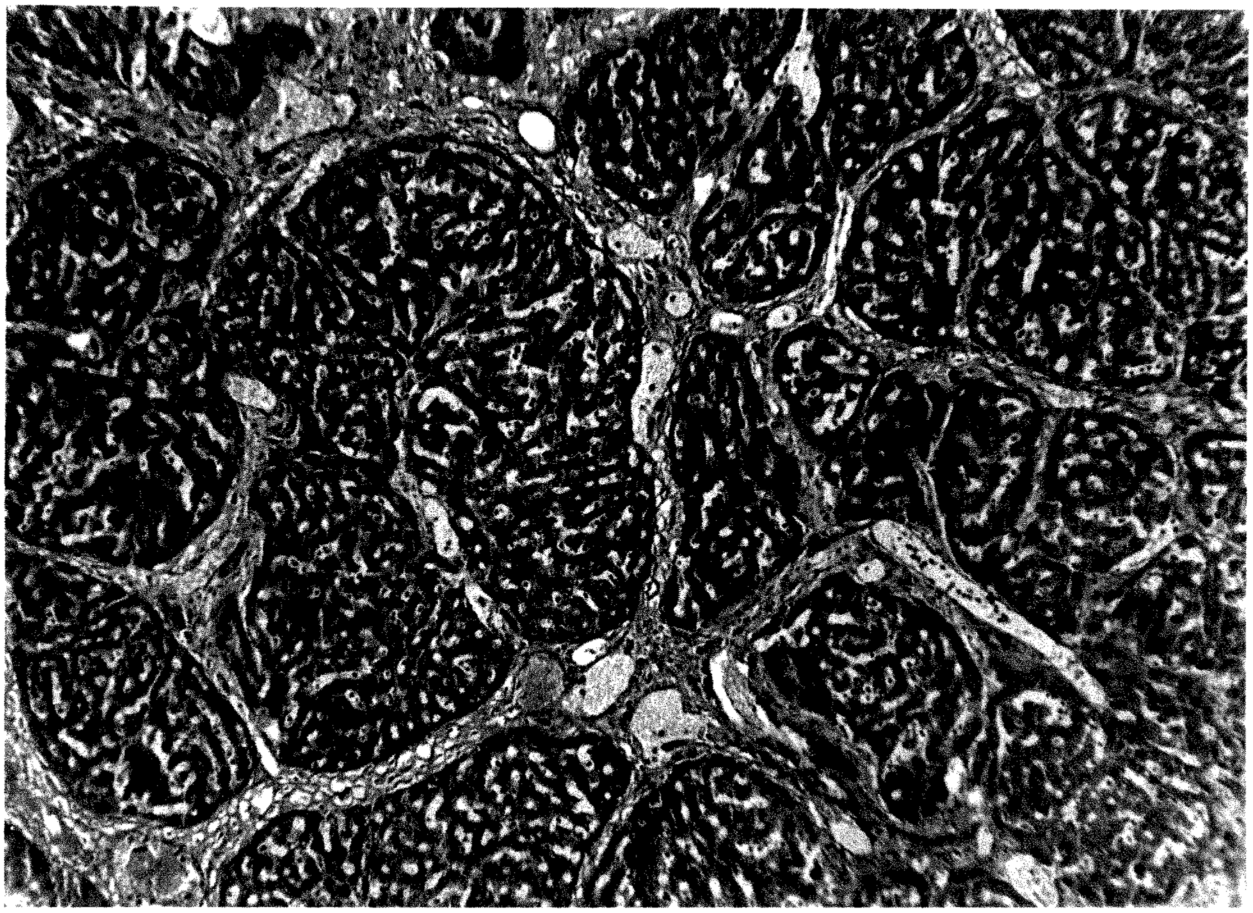


Figure 1. Trichrome-stained liver section of rat treated with carbon tetrachloride (× 100). The section is characteristic of the portal cirrhotic lesion with well-developed micronodules separated by thin fibrous trabeculae.

To overcome the problems of human studies, many investigators have developed animal models of cirrhosis (7–9). We recently refined such a model in the rat, which closely resembles human alcoholic cirrhosis, and used it to study the effects of halothane (5). In the present study we have extended this work by examining other drugs used in anesthetic practice. We found enflurane, isoflurane, and halothane at 1 MAC resulted in a mild but similar degree of acute liver dysfunction as indicated by small increases in SGOT and SGPT. However, the dysfunction was about the same as in noncirrhotic rats, suggesting that the presence of preexisting cirrhosis did not exacerbate the acute effects of any of these anesthetics on liver function. Fentanyl also produced mild liver dysfunction that was independent of the presence of cirrhosis. The detrimental effects of narcotics on liver function have been observed by other investigators (10,11).

Rats exposed to anesthetic and analgesic in this study were found to have only moderate degrees of cirrhosis. There remains the possibility that different results would occur in the presence of severe cirrhosis with a more advanced degree of liver dysfunction and portal hypertension. This notwithstanding, we could find no advantage for using one anesthetic over another or for using fentanyl in the presence of preexisting liver disease. However, the relatively large variance in the liver function tests together with the small group sizes and the multiple groups that were compared promote the likelihood that a $\beta$-type error may exist at the level of significance at which we were testing (12).

## References

1. Zakin D, Boyer TD, Montgomery C, Kanas N. Alcoholic liver disease. In: Zakin D, Boyer TD, eds. Hepatology. Philadelphia: W.B. Saunders, 1982:739–41.
2. Martin GA, Bode CH. The epidemiology of cirrhosis of the liver. In: Alcoholic cirrhosis and other toxic hepatopathies. Stockholm: Nordiska Bkhandelis Forag, 1970:315.
3. Schmidt W. The epidemiology of cirrhosis of the liver: a statistical analysis of mortality data with special reference to Can-

ada. In: Fisher MM, Rankin JC, eds. Alcohol and the liver. New York: Plenum Press, 1977:1–26.

4. French AB, Barss TP, Fairlie CS, Bengle AL, Jones CM, Linton BB, Beecher HK. Metabolic effects of anesthesia in man. V. A comparison of the effects of ether and cyclopropane on the abnormal liver. Ann Surg 1952;135:145–63.
5. Maze M, Smith CM, Baden JM. Halothane does not exacerbate liver dysfunction in cirrhotic rat. Anesthesiology 1985;62:1–5.
6. Scheuer PJ. Liver biopsy interpretation. Baltimore: Williams and Wilkins, 1968:55–69.
7. McLean EK, McLean AEM, Sutton PM. Instant cirrhosis: an improved method for producing cirrhosis of the liver in rats by simultaneous administration of carbon tetrachloride and phenobarbital. Br J Exp Pathol 1969;50:502–6.
8. Reuber MD, Glover EL. Cirrhosis and carcinoma of the liver in male rats given subcutaneous carbon tetrachloride. J Natl Cancer Inst 1970;44:419–27.
9. Trivedi P, Mowat AP. Carbon tetrachloride-induced hepatic fibrosis and cirrhosis in the developing rat: an experimental model of cirrhosis in childhood. Br J Exp Pathol 1983;64:25–33.
10. Needham WP, Shuster L, Kanel GC, Thompson ML. Liver damage from narcotics in mice. Toxicol Appl Pharmacol 1981;58:157–70.
11. Shingu K, Eger EI II, Johnson BH, Van Dyke RA, Lurz FW, Harper MH, Cheng A. Hepatic injury induced by anesthetic agents in rats. Anesth Analg 1983;62:140–5.
12. Freiman JA, Chalmers TC, Smith H, Kuebler RR. The importance of beta, the type II error and sample size in the design and interpretation of the randomized control trial. N Engl J Med 1978;299:690–4.

# Intravenous Lidocaine as a Suppressant of Coughing during Tracheal Intubation

Hidekazu Yukioka, MD, Noritada Yoshimoto, MD, Kiyoji Nishimura, MD, and Mitsugu Fujimori, MD

YUKIOKA H, YOSHIMOTO N, NISHIMURA K, FUJIMORI M. Intravenous lidocaine as a suppressant of coughing during tracheal intubation. Anesth Analg 1985;64:1189–92.

*Effects of intravenously administered lidocaine on cough suppression during tracheal intubation under general anesthesia were evaluated in two studies. In study 1, 100 patients received either a placebo or 0.5, 1.0, 1.5, or 2.0 mg/kg lidocaine intravenously 1 min before tracheal intubation. All visible coughs were classified as coughing. The incidence of coughing decreased as the dose of lidocaine increased. A dose of 1 mg/kg or more of intravenous lidocaine suppressed the cough reflex significantly ($P < 0.01$). Coughing was suppressed completely by 2 mg/kg of intravenous lidocaine. In study 2, 108 patients received 2 mg/kg lidocaine intravenously or a placebo 1, 3, 5, 7, 10, or 15 min before intubation. The same criteria for determining whether a patient did or did not cough during tracheal intubation were used as in study 1. The incidence of coughing decreased significantly ($P < 0.01$) when 2 mg/kg of lidocaine was injected intravenously between 1 and 5 min before our attempting intubation. Cough reflex was suppressed completely by plasma concentrations of lidocaine in excess of 3 μg/ml.*

Key Words: INTUBATION, TRACHEAL—intravenous lidocaine. ANESTHETICS, LOCAL—intravenous lidocaine.

It is well known that small intravenous doses of lidocaine suppress the cough reflex without serious side effects (1–4) during endotracheal intubation, extubation, bronchography, bronchoscopy, and laryngoscopy (1,2,5–7). The dose of lidocaine needed to suppress coughing during tracheal intubation under general anesthesia and the time it should be given have not, however, been defined. This study was designed to determine the optimal dose and the effective time of intravenous lidocaine for suppression of coughing during tracheal intubation under general anesthesia induced by a face mask with $N_2O$–halothane–$O_2$.

## Methods

The study included 208 ASA physical status I patients scheduled for orthopedic, urologic, gynecologic, and general surgery, whose ages ranged from 15–55 yr with a mean age of 38 yr and a mean weight of 53 kg. There were 46 men and 162 women. Informed consent was obtained from each patient, and the protocol was approved by the Institutional Human Studies Committee. Preanesthetic medications consisted of intramuscular atropine (0.5 mg) and either secobarbital (100 mg) or diazepam (10 mg) given intramuscularly 60–90 min before induction of anesthesia.

### *Study 1*

One hundred patients were assigned at random to one of five groups with 20 patients in each category. Anesthesia was induced by a face mask with 67% nitrous oxide and halothane in oxygen. Halothane concentration was increased gradually by 0.5% with each successive respiration and reached 3% within 30 sec. Respirations were spontaneous throughout the study. Lidocaine (0.5, 1.0, 1.5, or 2.0 mg/kg) or placebo (saline) was administered intravenously using a double blind technique. The staff anesthesiologist based observations that satisfactory surgical anesthesia had been reached on criteria including changes in respiratory pattern, the size of the pupils, and fixation of the eyeball in the central position. After the injection of lidocaine or placebo, respiration was assisted for 1 min, and the trachea then was intubated without

---

Received from the Department of Anesthesiology, Osaka City University Medical School, Osaka, Japan. Accepted for publication June 10, 1985.

Address correspondence to Dr. Yukioka, Department of Anesthesiology, Osaka City University, Medical School, 7-5-1, Asahimachi, Abeno-ku, Osaka, 545, Japan.

© 1985 by the International Anesthesia Research Society

Table 1. Induction Times and Intubation Times in Study 1[a]

| | Induction time (min) | Intubation time (sec) |
|---|---|---|
| Placebo | 10.4 ± 1.5[b] | 43.8 ± 15.1 |
| Lidocaine (intravenous) | | |
| 0.5 mg/kg | 10.2 ± 0.6 | 42.4 ± 11.1 |
| 1.0 mg/kg | 10.6 ± 1.1 | 44.7 ± 12.5 |
| 1.5 mg/kg | 10.6 ± 0.9 | 39.6 ± 11.3 |
| 2.0 mg/kg | 10.5 ± 1.1 | 46.0 ± 17.0 |

[a] $n$ = 20 in each group.
[b] Mean ± SD.

Table 2. Incidence of Coughing in Study 1

| | Incidence of coughing (%) |
|---|---|
| Placebo | 70 |
| Lidocaine (intravenous) | |
| 0.5 mg/kg | 65 |
| 1.0 mg/kg | 30 |
| 1.5 mg/kg | 20 |
| 2.0 mg/kg | 0 |

muscle relaxant, topical anesthetic, or stylet. Anesthesia was maintained with 67% nitrous oxide and 1% halothane in oxygen by manual ventilation for 2 min after tracheal intubation. Patients with difficult or esophageal intubation were eliminated from the study. Induction time of anesthesia (time from the application to removal of the face mask) and tracheal intubation time (time from removal of the face mask to the first manual ventilation after tracheal intubation) were measured. All visible coughs were classified as coughing. No attempt was made to evaluate the degree of severity of coughing. Data were analyzed using multiple comparisons as described by Goodman (8) and modified by Miller (9). This is an adaptation of Scheffé's F-projection to nominal data.

### *Study 2*

Anesthesia was induced by a face mask with nitrous oxide–halothane–oxygen as described in study 1. In study 2, induction time was, as determined in study 1, consistently 10.5 min. One hundred and eight patients received 2 mg/kg intravenous lidocaine or a placebo in a double-blind manner 1, 3, 5, 7, 10, or 15 min before removal of the face mask. The 108 patients were divided at random into six groups according to the administration time of 2 mg/kg intravenous lidocaine or the placebo, with 18 patients in each group. Each group of 18 patients consisted of 15 patients given 2 mg/kg intravenous lidocaine and 3 patients given the placebo. Respiration was assisted for 1 min before the removal of the face mask. The trachea was then intubated and anesthesia maintained with $N_2O$–$O_2$–halothane, as described in study 1. Patients with difficult or esophageal intubation were eliminated from the study. Intubation time was measured, and the same criteria as in study 1 were used for determining whether a patient did or did not cough during tracheal intubation.

From each group, four or five patients were selected at random for arterial blood sampling. Samples were withdrawn within 10 sec at intubation for measurement of plasma lidocaine concentrations by gas chromatographic analysis. The concentrations in the two groups of patients, those who coughed and those who did not, were compared using the "two-sample" $t$-test in the Minitab statistical package. Other data were analyzed using multiple comparisons, as described in study 1.

## Results

### *Study 1*

There were no significant differences among the groups in sex, age, weight or height. Induction time (average time, 10.5 min), intubation time (average time, 43.3 sec), and the incidence of coughing is shown in Tables 1 and 2. The incidence of coughing decreased as the dose of intravenous lidocaine increased. A dose of 1 mg/kg or more of intravenous lidocaine suppressed the cough reflex significantly ($P < 0.01$). Intravenous lidocaine in doses of 2 mg/kg suppressed the cough reflex completely.

### *Study 2*

There were no significant differences among the groups in sex, age, weight, or height. Intubation time, about 43 sec, was similar in all groups. The incidence of coughing and plasma concentrations of lidocaine are shown in Tables 3 and 4. Coughing was suppressed completely 1 min after injection of 2 mg/kg of lidocaine intravenously. At 3 and 5 min after injection, there was significant depression of the cough reflex ($P < 0.01$). At 7 min and thereafter, however, suppression of the cough reflex was no longer significant. The mean plasma concentration of lidocaine (mean ± SD) was significantly greater in those patients who did not cough (3.95 ± 1.76 μg/ml) than in those who did cough (2.30 ± 0.56 μg/ml) ($P < 0.01$). Coughing was completely suppressed by plasma lidocaine concentrations in excess of 3 μg/ml (Fig. 1). Serious side effects of intravenous lidocaine did not occur in either study 1 or 2.

Table 3. Incidence of Coughing in Study 2

| | Incidence of coughing (%) |
|---|---|
| 1 min[a] ($n$ = 15) | 0 |
| 3 min ($n$ = 15) | 13 |
| 5 min ($n$ = 15) | 13 |
| 7 min ($n$ = 15) | 33 |
| 10 min ($n$ = 15) | 53 |
| 15 min ($n$ = 15) | 53 |
| Placebo ($n$ = 18) | 67 |

[a] Time between administration of lidocaine, 2 mg/kg, and removal of the face mask.

Table 4. Arterial Plasma Concentrations of Lidocaine in Study 2

| Time[a] (min) | Lidocaine concentration[b] (μg/ml) |
|---|---|
| 1 ($n$ = 4) | 6.24 ± 1.51[c] |
| 3 ($n$ = 4) | 3.65 ± 1.12 |
| 5 ($n$ = 5) | 3.11 ± 0.52 |
| 7 ($n$ = 4) | 2.99 ± 0.49 |
| 10 ($n$ = 4) | 2.18 ± 0.78 |
| 15 ($n$ = 4) | 1.81 ± 0.63 |

[a] Time, time from administration of lidocaine, 2 mg/kg intravenously, to removal of the face mask.

[b] Lidocaine concentration, plasma concentration of lidocaine at the time of intubation.

[c] Mean ± SD.

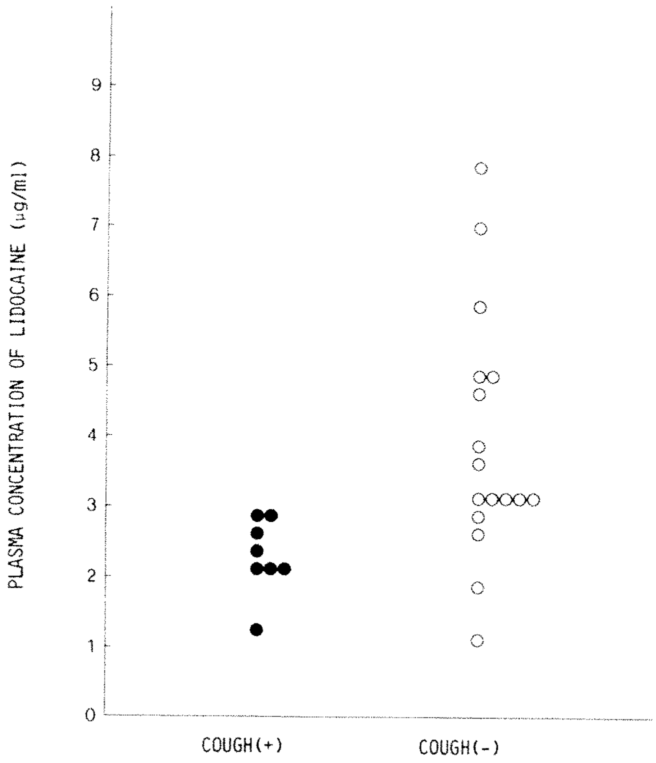


Figure 1. Plasma concentrations of lidocaine at the time of intubation in patients who did (+) and did not (−) cough.

## Discussion

There are many reports on the cough-suppressant effect of intravenous lidocaine. Steinhaus et al. (10), for example, reported that intravenous lidocaine suppresses the cough reflex produced by moving the endotracheal tube. Smith et al. (2) reported that a test dose of 2% lidocaine, 40 mg, followed by an additional 150–200 mg injected in less than 60 sec suppressed the cough reflex successfully for 8–9 min during bronchography after tracheal intubation with thiopental and succinylcholine. Although other investigators also reported successful cough suppression by intravenous lidocaine during tracheal intubation, extubation, bronchoscopy, and laryngoscopy (1,5–7) under general anesthesia, dose-dependent responses of intravenous lidocaine and the correlation of plasma concentration of lidocaine with cough suppression have not been examined in previous studies.

In the present study, the effect of intravenous lidocaine on cough suppression was increased in a dose-dependent manner and correlated well with plasma levels of lidocaine. Administration of 2 mg/kg intravenous lidocaine was effective in blocking the cough reflex during tracheal intubation with the patient under general anesthesia induced by a face mask with $N_2O$–halothane–$O_2$. Coughing was effectively eliminated by plasma concentrations of lidocaine in excess of 3 μg/ml.

Plasma concentrations of lidocaine after 2 mg/kg of intravenous lidocaine may be high enough to be associated with possible systemic toxicity. The lack of side effects in this study may be related to the fact that the patients were under general anesthesia.

It is concluded that the optimal dose of lidocaine is 2 mg/kg intravenously for the suppression of coughing stimulated by tracheal intubation after induction of anesthesia with nitrous oxide and halothane. The data also indicate that intravenous lidocaine suppresses the cough reflex effectively without serious side effects if patients are well anesthetized.

## References

1. Steinhaus JE, Gaskin L. A study of intravenous lidocaine as a suppressant of cough reflex. Anesthesiology 1963;24:285–90.
2. Smith FR, Kundahl PC. Intravenously administrated lidocaine as cough depressant during general anesthesia for bronchography. Chest 1973;63:427–9.
3. Poulton TJ, James FM. Cough suppression by lidocaine. Anesthesiology 1979;50:470–2.
4. Christensen V, Ledegaard-Pedersen HJ, Skovsted P. Intravenous lidocaine as a suppressant of persistent cough caused by bronchoscopy. Acta Anaesthesiol Scand [Suppl] 1978;67:84–6.
5. Blancato LS, Peng ATC, Alonsabe D. Intravenous lidocaine as an adjunct to general anesthesia for endoscopy. Anesth Analg 1969;48:224–7.

6. Baraka N. Intravenous lidocaine controls extubation laryngospasm in children. Anesth Analg 1978;57:506–7.
7. Gefke K, Andersen LW, Friesel E. Lidocaine given intravenously as a suppressant of cough and laryngospasm in connection with extubation after tonsillectomy. Acta Anaesthesiol Scand 1983;27:111–2.
8. Goodman LA. Simultaneous confidence intervals for contrasts among multinomial populations. Ann Math Statist 1964; 35:716–25.
9. Miller RG Jr. Simultaneous statistical inference. New York: McGraw-Hill Book Co, 1966: 218.
10. Steinhaus JE, Howland DE. Intravenously administered lidocaine as a supplement to nitrous oxide–thiobarbiturate anesthesia. Anesth Analg 1958;37:40–6.

ANESTH ANALG 1985;64:1193–6

# Does Intravenous Lidocaine Prevent Laryngospasm after Extubation in Children?

Pernille Leicht, MD, Torben Wisborg, MD, and Bent Chraemmer-Jørgensen, MD

LEICHT P, WISBORG T, CHRAEMMER-JØRGENSEN B. Does intravenous lidocaine prevent laryngospasm after extubation in children? Anesth Analg 1985;64:1193–6.

*One hundred otherwise healthy children undergoing tonsillectomy were investigated in a double-blind study to examine the effect of intravenous lidocaine in preventing laryngospasm upon extubation. The children were anesthetized with $N_2O$–$O_2$–halothane and orally intubated. They were randomly given lidocaine, 1.5 mg/kg, or saline intravenously prior to extubation, which took place at the same depth of anesthesia, namely when there were signs of swallowing activity. Eleven children (2%) in each group of 50 developed laryngospasm. From our findings it is concluded that lidocaine, 1.5 mg/kg, does not prevent laryngospasm upon extubation when extubation is carried out at the start of swallowing activity.*

Key Words: ANESTHESIA—otolaryngologic. LARYNX—spasm. ANESTHETICS, LOCAL—lidocaine intravenously.

Intravenous lidocaine has been shown to suppress effectively persistent cough caused by bronchoscopy (1). Lidocaine, given topically to the larynx and trachea (2) or intravenously (3), has been shown to blunt the increases in heart rate and blood pressure associated with laryngoscopy and endotracheal intubation. The data of Hamill et al. (4) indicated that lidocaine prevented intracranial hypertension after intubation and also limited the intensity and duration of cardiovascular stimulation. Furthermore, they showed that the intravenous route was the preferred technique for administering lidocaine. Bidwai et al. (5) demonstrated that intravenous lidocaine prevented coughing and increases in blood pressure and heart rate during and after endotracheal extubation. Adenotonsillectomy, a brief surgical procedure, can present major acute problems of bleeding, airway obstruction, and cardiac arrhythmias. As a consequence, the patient must have a rapid return to responsiveness with intact protective airway reflexes before tracheal extubation. Occasionally, this procedure is followed by laryngospasm, a serious complication, which is almost always associated with airway manipulation by the anesthesiologist or with the presence of foreign material in the larynx of the lightly anesthetized patient. In an open study including 40 children undergoing tonsillectomy, Baraka (6) showed that intravenous lidocaine prevented extubation laryngospasm. The purpose of this controlled clinical trial using double-blind technique was, therefore, to confirm or reject the asserted prophylactic effect of lidocaine against laryngospasm after tracheal extubation.

## Material and Methods

One hundred otherwise healthy children older than 1 yr of age and with a body weight less than 40 kg scheduled for elective tonsillectomy under general anesthesia participated in the study. Children with known hypersensitivity to lidocaine were not included. The study protocol was approved by the Copenhagen County Human Investigation Committee. Informed consent was obtained from the parents of all participating children.

All the children were premedicated half an hour prior to expected induction of anesthesia by intramuscular injection of 0.05 ml/kg body weight of a solution containing meperidine, 28 mg/ml, chlorpromazine, 7 mg/ml, and promethazine, 7 mg/ml. Induction of anesthesia was performed by inhalation of $N_2O$–$O_2$–halothane by face mask followed by orotracheal intubation without the use of a muscle relaxant. Anesthesia was maintained with $N_2O$–$O_2$ (50% each) and halothane as needed. Ventilation was controlled manually using a Bain system. All the children had

---

Received from the Department of Anesthesia, Glostrup Hospital, University of Copenhagen, Glostrup, Denmark. Accepted for publication June 10, 1985.

Address correspondence to Dr. Chraemmer-Jørgensen, Department of Anesthesia, Glostrup Hospital, University of Copenhagen, DK-2600, Glostrup, Denmark.

© 1985 by the International Anesthesia Research Society

an intravenous cannula placed after induction of anesthesia, and the ECG was continuously monitored throughout the procedure. In case of bradycardia, atropine, 0.01 mg/kg body weight, was given intravenously. At the end of surgery, halothane was discontinued, and the child was ventilated with $N_2O–O_2$ (50% each) for 5 min, aiming at normoventilation. The pharynx was suctioned thoroughly and inspected for bleeding, and for the next 5 min the child was ventilated with $N_2O–O_2$ (50% each), aiming at spontaneous breathing. When spontaneous ventilation was achieved and 10 min had passed after discontinuation of halothane, the $N_2O$ was turned off and an injection of 0.15 ml/kg of a solution drawn from a neutrally marked vial containing either lidocaine, 10 mg/ml (1%), or normal saline was given intravenously according to the allocation, the injection lasting 1 min. It was the intention to extubate the child after a minimum of 1 min when the child was still breathing spontaneously and had started swallowing. The time from the end of the 1 min injection of lidocaine–saline until extubation was recorded in all children. Laryngospasm was defined as a condition occurring within 2 min after extubation and characterized by the following findings, the severity of which were graded on a three point scale: 1, stridor on inspiration; 2, total occlusion of the cords (silence with no air movement); and 3, cyanosis. Children who developed laryngospasm were treated on the basis of the following principles according to the severity of symptoms: 1, positive pressure ventilation with 100% $O_2$; 2, suctioning of the pharynx; 3, intravenous atropine; 4, intravenous succinylcholine; and 5, reintubation.

The results were evaluated statistically using the $\chi^2$ test with the correction of Yates for comparison of qualitative variables. The *t*-test was used for comparison of quantitative variables. The chosen level of significance was $2\alpha = 5\%$. When planning the study the sample size ($n$) was calculated (7) according to the acceptance of a type II error ($\beta$) of 10% and a clinically meaningful difference ($\Delta$) of 20% (in the control group Baraka (6) had 4 children (20%) with laryngospasm). The sample size was estimated to 90 and finally $n$ = 100 was chosen. All the data are given as median values with interquartile values in parentheses.

## Results

There were no differences between groups concerning sex, age, weight, and duration of surgery (Table 1). Eleven children (22%) in each group developed laryngospasm, the severity of which is shown in Figure 1. The median time from the end of the 1-min injection of lidocaine or saline to extubation for all the children was 4.5 min (3–6 min). For children given lidocaine and subsequently developing laryngospasm, the median interval was 4.5 min (4–5 min). For children given lidocaine and not developing laryngospasm, the median interval was 5 min (4–7.5 min). In children given saline, the median interval was 4.5 (3.5–6.0 min) (laryngospasm) and 4.0 min (2–5.5 min) (no laryngospasm), respectively. There were no significant differences in time interval among the groups and subgroups. The severity of the observed laryngospasms was almost identical in the two groups (Fig. 1).

Table 1. Sex, Age, Weight, and Duration of Surgery for the Children Investigated

| | Lidocaine group | Placebo group |
|---|---|---|
| *n* | 50 | 50 |
| Female:male | 21:29 | 18:32 |
| Age (yr) | 5 (4–6) | 5 (3–7) |
| Weight (kg) | 19.6 (16.8–23.0) | 20.0 (17.0–27.3) |
| Duration of surgery (min) | 20.0 (15.0–22.5) | 20.0 (15.0–25.0) |

Data are given as median values with interquartile values in parentheses.

All episodes of laryngospasm were successfully treated with positive pressure ventilation with oxygen and suctioning of the pharynx. None of the children had to be paralyzed or reintubated. No complications, including apnea, were seen during and after the injection of lidocaine.

## Discussion

Laryngospasm is a frequent complication after extubation of children after tonsillectomy. We found the incidence to be 22%, which is in agreement with the findings of Baraka (6). In an open study he showed that lidocaine, 2 mg/kg, injected 1 min prior to extubation totally prevented extubation laryngospasm in 20 children undergoing tonsillectomy. In the control group, 4 out of 20 children developed severe laryngospasm after extubation, though this difference is not statistically significant at the 5% level, $\chi^2 = 2.5$ ($P > 0.1$) ($\chi^2$ test corrected for continuity) (8).

No differences between groups in incidence and/or severity of laryngospasm were seen at the dosage and timing regimen pursued in our study. In Baraka's study, the children were extubated 1 min after the injection of lidocaine—by the clock rather than any specific clinical signs of his or her level of consciousness. Baraka's subjects must have been on the steep upslope of an emergence curve while this was happening. Because intravenous lidocaine also has cen-

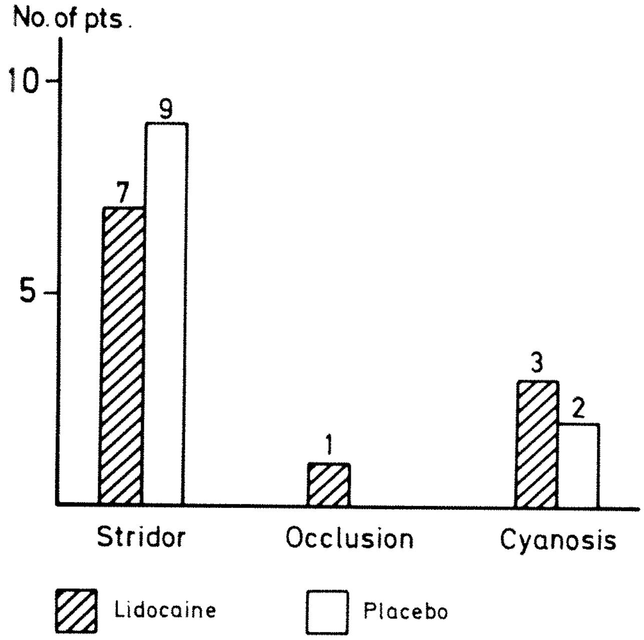


Figure 1. Severity of observed laryngospasms. For further explanation see text.

tral effects (9,10), it may well have returned the "test" children to a deeper plane of anesthesia so that they were extubated relatively "deep" as opposed to the control children being extubated "light." Therefore, it is possible that Baraka's protection had more to do with differences in "central" depth of anesthesia than differences in peripheral reflex responsiveness of the upper airway. In our study all children were extubated not at a fixed time, but rather at a consistent clinical indicator of depth of anesthesia, i.e., start of swallowing.

Although differences in time intervals were not statistically significant, it is notable that the interquartile interval in those receiving lidocaine was 4–7.5 min while the control times to extubation (start of swallowing) were 2–6.0 min. These numbers are consistent with the concept that lidocaine has some anesthetizing properties (9,10), and therefore, it takes longer for that group to reach the particular level of consciousness used as the end-point for timing of extubation in this study.

Investigating 80 adult patients undergoing a variety of elective surgery, Bidwai et al. (5) demonstrated that intravenous injection of lidocaine, 1 mg/kg, administered 2 min before endotracheal extubation prevented coughing and increases in blood pressure and heart rate during and after extubation. Abou-Madi et al., studying 30 male patients scheduled for elective surgery (3), found that lidocaine, 1.5 mg/kg, injected 2–3 min prior to intubation gave better protection against cardiac arrhythmias, hypertension, and tachycardia than lidocaine, 0.75 mg/kg. Lidocaine blood levels of 3–6 $\mu$g/ml are known to potentiate the effects of nitrous oxide anesthesia in humans (10). A 10–28% reduction in halothane MAC has been observed in dogs with blood lidocaine levels between 3 and 10 $\mu$g/ml. Bedford et al. (11) demonstrated that lidocaine prevented an increase in intracranial pressure after endotracheal intubation. They observed a mean blood lidocaine level of 3.2 $\mu$g/ml 1.5 min after 1.5 mg/kg intravenously. Thus it appears that the effect of lidocaine in preventing coughing upon extubation or in diminishing the increase in blood pressure and heart rate after in- or extubation or preventing an increase in ICP after intubation is dependent on a sufficient concentration of lidocaine in the blood. Consequently, the protective effect of lidocaine reported by others may reflect at least partially additional central nervous system depression (i.e., deeper anesthesia) produced by the local anesthetic. Because lidocaine is rapidly eliminated from the blood (12), the timing of in- or extubation in relation to timing and doses of lidocaine seems crucial. From our findings it is concluded that lidocaine, 1.5 mg/kg, intravenously does not prevent laryngospasm upon extubation when extubation is carried out at the beginning of swallowing activity. Rather, to derive advantage from the central nervous system depression produced by lidocaine, one must extubate before signs of swallowing activity.

## References

1. Christensen V, Ladegaard-Pedersen HJ, Skovsted P. Intravenous lidocaine as a suppressant of persistent cough caused by bronchoscopy. Acta Anaesthesiol Scand 1978;suppl. 67:84–6.
2. Denlinger JK, Ellison N, Ominsky AJ. Effects of intratracheal lidocaine on circulatory responses to tracheal intubation. Anesthesiology 1974;41:409–12.
3. Abou-Madi MN, Keszler H, Yacoub JM. Cardiovascular reactions to laryngoscopy and tracheal intubation following small and large intravenous doses of lidocaine. Can Anesth Soc J 1977;24:12–9.
4. Hamill JF, Bedford RF, Weaver DC, Colohan AR. Lidocaine before endotracheal intubation: Intravenous or laryngotracheal? Anesthesiology 1981;55:578–81.
5. Bidwai AV, Bidwai VA, Rogers CR, Stanley TH. Blood pressure and pulse rate responses to endotracheal extubation with and without prior injection of lidocaine. Anesthesiology 1979;51:171–3.
6. Baraka A. Intravenous lidocaine controls extubation laryngospasm in children. Anesth Analg 1978;57:506–7.
7. Feinstein AR. Clinical biostatistics—XXXIV. The other side of "statistical significance": alpha, beta, delta, and the calculation of sample size. Clin Pharmacol Ther 1975;18:491–505.
8. Siegel S. Nonparametric statistics for the behavioral sciences. New York, NY: McGraw-Hill, 1956.
9. Phillips OC, Lyons WB, Harris LC, Nelson AT, Graff TD, Fra-

zier TM. Intravenous lidocaine as an adjunct to general anesthesia: a clinical evaluation. Anesth Analg 1960;39:317–22.

10. Himes RS, DiFazio CA, Burney RG. Effects of lidocaine on the anesthetic requirements for nitrous oxide and halothane. Anesthesiology 1977;47:437–40.

11. Bedford RF, Winn HR, Tyson G, Park TS, Jane JA. Lidocaine prevents increased ICP after endotracheal intubation. In Shulman K, Mamarou A, Miller JD, Becker DP, Hochwald GM, Brock M, eds. Intracranial pressure IV. Berlin: Springer, 1980:595–8.

12. Patel RI, Peterson RG, Aldrete JA. Endotracheal compared with intravenous injection of 3 mg/kg of lignocaine. Measurement of arterial and venous levels. Anaesthesia 1981;36:772–4.

ANESTH ANALG
1985;64:1197–201

# Decreased Incidence and Mortality of Anaphylaxis to Chymopapain

Jonathan Moss, MD, PhD, Michael F. Roizen, MD, Eugene J. Nordby, MD, Ronald Thisted, PhD, Jeffrey L. Apfelbaum, MD, Bruce D. Schreider, MD, PhD, and Daniel J. McDermott, PhD

MOSS J, ROIZEN MF, NORDBY EJ, THISTED R, APFELBAUM JL, SCHREIDER BD, McDERMOTT DJ. Decreased incidence and mortality of anaphylaxis to chymopapain. Anesth Analg 1985;64:1197–201.

*A recognized side effect of chemonucleolysis is life-threatening anaphylaxis to chymopapain. In the clinical trials of chymopapain, 13 cases of anaphylaxis were reported in 1585 administrations (0.82%). Two patients died. Data from a postmarketing survey (48,239 questionnaires) were reviewed to identify factors influencing the incidence and severity of anaphylaxis. The results indicate the incidence of anaphylaxis decreased to 0.44% in the 1983–1984 period (126/23,736), a level significantly ($P \leq 0.001$) below the incidence of 0.82% observed in initial clinical trials. Only three deaths from complications related to anaphylaxis occurred in approximately 75,000 administrations (producing 252 anaphylactic episodes) reported since December 1982. The prophylactic use of antihistamines and pretreatment with intravenous fluids coincide with the dramatic reduction in mortality due to anaphylaxis. However, overdiagnosis of anaphylaxis in the clinical trials and avoidance of chemonucleolysis in patients with IgE antibodies to chymopapain may account, in part, for the reduction in incidence.*

Key Words: ALLERGY—chymopapain. SURGERY, NEUROLOGIC—chymopapain.

Chemonucleolysis is the dissolution of the herniated nucleus pulposus by injection of the enzyme chymopapain. Chemonucleolysis was first employed over two decades ago in humans with herniated intervertebral disks (1,2). This technique fell into disfavor because the only well-controlled and double-blind clinical trial found no appreciable difference between chymopapain and placebo regarding the incidence of or improvement in herniated lumbar disks (3). Results from this study were biased by certain practices in patient selection, deficiencies in study design, and the fact that enzyme activators were present in the placebo (4). However, in 1982, studies in the US using a different preparation of chymopapain (Chymodiactin, Smith Laboratories, Northbrook, IL) demonstrated that chemonucleolysis was vastly more effective than placebo in relieving symptoms in patients who were candidates for laminectomy (5). In these and additional investigations, over 1580 patients were studied. All patients were given general anesthesia. Thirteen had severe anaphylactic or anaphylactoid reactions (6).

Since FDA approval in November 1982, over 75,000 patients in the United States have been given Chymodiactin. To study the incidence of anaphylaxis, as well as the factors influencing the incidence and severity of anaphylaxis, we requested each surgeon performing chemonucleolysis to complete a postmarketing surveillance questionnaire. Responses to these questionnaires demonstrate a dramatic decrease in the rate of anaphylaxis since 1982 and an even more dramatic decrease in mortality due to anaphylaxis since 1982.

## Methods

For the approximately 75,000 doses of chymopapain marketed by May 31, 1984, 48,239 postmarketing surveillance questionnaires were voluntarily completed. This number included 2678 reports that were supple-

---

Supported in part by IPOI #AG 03104-03, 04.

Presented in part at the annual scientific meeting of the International Anesthesia Research Society, New Orleans, March 1983.

Received from the Department of Anesthesiology, Harvard Medical School, Boston, Massachusetts; the Departments of Anesthesia, Medicine, and Pharmacology, University of California, San Francisco, California; the Department of Surgery, University of Wisconsin, Madison, Wisconsin; the Departments of Statistics and Anesthesia & Critical Care, University of Chicago, Chicago, Illinois; and Smith Laboratories, Northbrook, Illinois. Accepted for publication July 2, 1985.

Address correspondence to Dr. Moss, Department of Anesthesia & Critical Care, 5841 S. Maryland Ave., Box 428, University of Chicago's Pritzker School of Medicine, Chicago, IL 60637.

© 1985 by the International Anesthesia Research Society

mented by an additional survey to collect data not completed on the initial questionnaire. Forms that were incomplete (e.g., those failing to specify type of anesthesia or sex of patient) were excluded from analysis if no anaphylactic event was reported. Data sought by these questionnaires included the age and sex of the patient; the use of premedicants; type of anesthesia administered [local (with or without supplements), regional, or general]; anesthetic agents administered; the occurrence and symptoms of an anaphylactic or anaphylactoid reaction; and, if a reaction did occur, patient outcome.

The periods of study were as follows: Period 1 consists of the time before FDA approval of Chymodiactin (that is, the time prior to November 1982). Period 2 consists of the time after FDA approval but prior to widespread use of immunologic screening tests to identify patients who might be excluded from undergoing chemonucleolysis (December 1982 to September 27, 1983). Period 3 consists of the time after the widespread use of such tests (September 28, 1983 to June 25, 1984).

No criteria other than the surgeon's judgment (and his or her reliance on the anesthetist's own criteria) were used to determine the presence of an anaphylactic reaction. Each form reporting anaphylaxis prompted inquiry to the surgeon about the nature and outcome of the reaction. Data were analyzed for statistical significance using two-sided binomial comparisons or the Fisher exact test (7).

## Results

The patients given Chymodiactin after FDA approval (periods 2 and 3) were similar in age and sex to those treated in the clinical trial (period 1), but they differed in several important aspects (Table 1). In periods 2 and 3, 93 and 91%, respectively, of patients were given $H_1$ and $H_2$ histamine antagonists prophylactically before administration of Chymodiactin. Only 17% of patients in period 1 were given either or both an $H_1$ and $H_2$ antagonist.

Across the three study periods, the incidence of anaphylaxis decreased significantly. This decrease was apparent in both male and female patients, regardless of the type of anesthetic given (Table 1). Between the clinical trial period (period 1) and the two post-FDA-release periods (periods 2 and 3), the rate of deaths from anaphylaxis decreased significantly (Table 1).

## Discussion

Chemically mediated anaphylactoid reactions during anesthesia have been studied systematically in humans (8–10). However, the unpredictability of anaphylactic reactions has limited the systematic study of anaphylaxis. The use of a common antigen, Chymodiactin, in a surgical setting affords physicians the opportunity to identify factors influencing the incidence and severity of anaphylaxis.

In the initial evaluation of chymopapain, laryngeal edema in two patients promoted the suggestion that chemonucleolysis be performed with the aid of general anesthesia. It is interesting to note that this procedure had been performed successfully under local anesthesia in Canada (11). Response to postmarketing surveillance questionnaires seemed to demonstrate an advantage of local anesthesia with standby by virtue of a decreased occurrence of anaphylaxis (Table 1). However this advantage, which occurred during period 2, disappeared as the overall rate of anaphylaxis decreased in period 3. Several explanations are possible for the apparent decreased rate of anaphylaxis in period 2 during local (as opposed to general) anesthesia, and for the subsequent clinical experience in which this advantage disappears. Perhaps the most likely cause of these changes is the overreporting of anaphylactic events. For example, patients under general anesthesia may receive more attentive monitoring. Small changes in blood pressure and heart rate may be noted more quickly and reported as a reaction in more attentively monitored patients. In addition, overly vigilant interpretation of cardiovascular signs occurring with general anesthesia (particularly with commonly used inhalational agents) could be a source of error. During operations other than chemonucleolysis, these changes in systemic vascular resistance, blood pressure, and heart rate probably would be interpreted as normal variants of an anesthetic technique. In addition, most surgeons perform their first set of chemonucleolytic procedures using general anesthesia. The initial suspicions and vigilance toward adverse reactions with chemonucleolysis may lead to overreporting in a surgeon's or anesthetist's early experience with chemonucleolysis.

Another explanation for the apparent initial lower rate of anaphylaxis during local anesthesia may reflect the effects of general anesthetics on the sympathoadrenal axis (12). The release of histamine that occurs during anaphylaxis markedly decreases systemic vascular resistance. This decrease elicits a compensatory sympathoadrenal response (13,14). Treatment of anaphylaxis with epinephrine is an attempt to mimic the body's response to anaphylaxis. Concomitant administration of $\beta$-adrenergic antagonists may potentiate anaphylaxis (15). Thus relatively minor reactions may be perpetuated by the blockade of the sympathoadrenal axis that occurs with inhalational anesthetics. Halothane and other anesthetics appear able to block sympathoadrenal release and to attenuate the re-

Table 1. Anaphylaxis to Chymopapain/Chymodiactin in Patients Undergoing Chemonucleolysis

| | Period 1 (Clinical trials) | Period 2 (December 1982 to September 27, 1983) | Period 3 (September 28, 1983 to June 25, 1984) |
|---|---|---|---|
| Estimated number of patients | 1585 | 30,000 | 45,000 |
| Mean age (yr) | 39 | 41 | 39 |
| Ratio of males to females (%) | 1049/536<br>(66.2) | 10,408/5769<br>(64.3) | 17,377/11,359<br>(60.5) |
| Number of questionnaires returned | 1585 | 16,177 | 28,736 |
| Number of anaphylactic events (%) | 13<br>(0.82) | 126<br>(0.78) | 126<br>(0.44) |
| Anaphylactic events/number of females given chymopapain and general anesthesia (%) | 11/536<br>(2.05) | 65/4182[a]<br>(1.55) | 67/8755[a]<br>(0.77) |
| Anaphylactic events/number of females given chymopapain and local anesthesia (%) | Local anesthesia not used | 15/1587<br>(0.95) | 14/2604<br>(0.54) |
| Anaphylactic events/number of males given chymopapain and general anesthesia (%) | 2/1049<br>(0.20) | 39/7410[a,b]<br>(0.53) | 37/13,549[a]<br>(0.27) |
| Anaphylactic events/number of males given chymopapain and local anesthesia (%) | Local anesthesia not used | 7/2998[b]<br>(0.23) | 8/3828<br>(0.21) |
| Percentage pretreated with $H_1$ and $H_2$ histamine antagonists | 17 | 93 | 91 |
| Number of deaths | 2[c] | 2[c] | 1[c] |
| Mortality rate due to anaphylaxis | 0.00126 | 0.00006 | 0.00002 |
| Percentage of anaphylactic reactions resulting in death | 15.4 | 1.6 | 0.8 |

[a] Significant ($P \le 0.001$) difference between periods 2 and 3.
[b] Significant ($P \le 0.05$) difference between general and local anesthesia.
[c] Significant ($P \le 0.05$) difference between period 1 and periods 2 and 3.
All other observed differences were not statistically significant.

sponse to changes in systemic vascular resistance in a dose-dependent fashion (16–18).

The data in this study demonstrate that a decrease in the rate of anaphylaxis may not be an argument for using local anesthesia with supplement instead of general anesthesia. It is clear, however, that local anesthesia does not increase the risk of anaphylaxis or of mortality from anaphylaxis. Indeed, an argument for using local anesthesia in chemonucleolysis exists. The vast majority of reported neurologic complications of chemonucleolysis occurred when the procedure was performed under general anesthesia (DJ McDermott, personal communication). These complications usually have been attributed to poor placement of the needle and the consequent introduction of radiocontrast material, enzyme, or both into the intrathecal space. Use of local anesthesia with sedation mandates that the practitioner place the needle into the disk with great facility lest patient dissatisfaction or discomfort require aborting the procedure.

No explanation can be advanced with certainty for the initial decrease in the rate of anaphylaxis and the subsequent similarity in rates during local as opposed to general anesthesia. Study would be required to confirm the explanation that we favor, a misreporting of anaphylactic events. This initial overreporting could have contributed to the decreased rate of anaphylactic reactions that has been reported over the time period examined. The reported rate of anaphylaxis decreased from 0.82% in period 1 to 0.78% in period 2 and to 0.44% in period 3. Patients given Chymodiactin after FDA approval differed from those treated in the clinical trials regarding pretreatment with antihistamines. In periods 2 and 3, 93 and 91%, respectively, of the patients were given $H_1$ and $H_2$ receptor antagonists prophylactically before administration of Chymodiactin. This practice was based on observations of the efficacy of prophylactic administration of antihistamines in attenuating anaphylactoid reactions (19). The 92% usage rate after FDA release contrasts with the 17% usage rate in the clinical trials. Is the decrease in anaphylaxis incidence attributable to the definition of anaphylaxis becoming more specific as experience using chymopapain accumulated, or to actual effectiveness of pretreating patients with antihistamines or intravenous fluids? Although no definitive answers exist, some information shedding light on these questions is available.

The largest reduction in the incidence of anaphylaxis occurred from September 1983 to June 1984; during this time pretreatment with antihistamines remained roughly constant (93–91%). However, it is important to note that although two patients of the 13 who had anaphylaxis in the clinical trials died, only three deaths attributable to anaphylaxis were reported in the subsequent 75,000 administrations. (All deaths attributable to anaphylaxis occurred in patients given general anesthesia.) The decrease in mortality is not due to a decreased incidence of anaphylaxis, because mortality decreased during period 2 and anaphylaxis incidence decreased most dramatically in period 3. Thus while prophylactic administration of antihistamines may not significantly reduce the overall rate of anaphylaxis, their use may be a significant factor in reducing mortality attributable to anaphylactic reactions. Alternatively, better physician awareness about recognizing and treating anaphylaxis may be a significant factor in the dramatic decrease in mortality. In fact, the manufacturer of Chymodiactin placed major emphasis on physician education.

The factor that did change from period 2 to period 3 (the time when the incidence of anaphylaxis decreased most) was patient selection. Perhaps some reduction in the frequency of allergic reactions reflects patient selection. Patients found to have elevated levels of circulating antibodies to chymopapain often were excluded from chemonucleolysis. However, immunologic tests were not in widespread use until September 1983 and thus could not have influenced the rate of anaphylaxis until after that date (11,19–21). Subsequent use of such tests may have influenced overall reaction rates. The choice of local or general anesthesia probably would not be influenced by the antibody test. In fact, the reduction in anaphylaxis rates occurs with local or general anesthesia to the same extent ($P \leq 0.001$) during time period 3.

Another difference between the data from the clinical trials and the data from postmarketing surveillance questionnaires is that the former pertained to a limited geographic region (98% of the clinical trials occurred in the state of Illinois), whereas the postmarketing data were derived from 1500 institutions throughout the US (22). Perhaps the overall rate of anaphylaxis to chymopapain varies significantly according to geography.

Thus this survey documented a decrease in the incidence and severity of anaphylaxis after use of chymopapain. These decreases are independent of the type of anesthesia employed. In addition, no relationship between the incidence of anaphylaxis and the prophylactic use of antihistamines is evident. However, the prophylactic use of antihistamines may account, in part, for the decreased mortality secondary to anaphylaxis. Other possible causes for the decreased mortality rate included vigorous preoperative fluid administration, patient selection (e.g., exclusion of high-risk patients by immunologic tests), and physician education. The most likely explanations for the decreasing incidence of anaphylaxis during the study periods include overreporting of anaphylaxis in earlier periods, the increased use of prophylactic measures, and more careful selection of patients for chemonucleolysis (due to the introduction of immunologic tests identifying patients at risk).

This survey accentuates the frustration of retrospective studies; they only can indicate areas to study and possible causes and rarely lead to clear answers. Although this retrospective study of chemonucleolysis identifies a decrease in the incidence and mortality due to anaphylactic reactions to chymopapain, its implications may have more widespread applicability and significance for management of reactions to radiocontrast media. In 1986, approximately 18 million procedures in the US will use contrast media; the mortality for these procedures may approximate 1000 patients (23). Although the actual mechanism of chymopapain hypersensitivity is mediated immunologically, and reactions to contrast material appear to involve several mechanisms, prospective studies might examine the usefulness of a similar approach involving fluid loading and prophylactic administration of antihistamines in patients having injections of contrast material (24,25).

## References

1. Smith L. Enzyme dissolution of the nucleus pulposus in humans. JAMA 1964;187:137.
2. Smith L, Brown JE. Treatment of lumbar intervertebral disc lesions by direct injection of chymopapain. J Bone Joint Surg (Br) 1967;49:502–19.
3. Schwetschenau PR, Ramirez A, Johnston J, Wiggs C, Martins AN. Double-blind evaluation of intradiscal chymopapain for herniated lumbar discs. Early results. J Neurosurg 1976;45:622–7.
4. Javid MJ. Treatment of herniated lumbar disk syndrome with chymopapain. JAMA 1980;243:2043–8.
5. Javid MJ, Nordby EJ, Ford LT, et al. Safety and efficacy of chymopapain (Chymodiactin) in herniated nucleus pulposus with sciatica. JAMA 1983;249:2489–94.
6. Moss J, Roizen MF. Adverse reactions to chemonucleolysis: anesthetic considerations. Int Anesthesiol Clin, in press.
7. Cox DR. The analysis of binary data. London: Methuen, 1970;48–52.
8. Moss J, Rosow CE. Histamine release by narcotics and muscle relaxants in humans. Anesthesiology 1983;59:330–9.
9. Lorenz W, Doenicke A. Histamine release in clinical conditions. Mt Sinai J Med 1978;45:357–86.
10. Stoelting RK. Allergic reactions during anesthesia. Anesth Analg 1983;62:341–56.
11. Hall B, McCulloch JA. Anaphylactic reactions following the intradiscal injection of chymopapain under local anesthesia. J Bone Joint Surg 1983;65-A:1215–9.
12. Roizen MF, Moss J, Muldoon SM. The effects of anesthesia, anesthetic adjuvant drugs, and surgery on plasma norepinephrine. In: Ziegler MG, Lake CR, eds. Norepinephrine. Baltimore:Williams and Wilkins, 1984:227–49.

13. Moss J, Fahmy NR, Sunder N, Beaven MA. Hormonal and hemodynamic profile of an anaphylactic reaction in man. Circulation 1981;63:210–3.

14. Hamberger B, Fredholm BB, Farnebo LO. Anaphylaxis and plasma catecholamines. Life Sci 1980;26:1465–71.

15. Jacobs RL, Rake GW Jr, Fournier DC, Chilton RJ, Culver WG. Potentiated anaphylaxis in patients with drug-induced beta-adrenergic blockade. J Allergy Clin Immunol 1981;68:125–7.

16. Roizen MF, Moss J, Henry DP, Kopin IJ. Effects of halothane on plasma catecholamines. Anesthesiology 1974;41:432–9.

17. Roizen MF, Horrigan RW, Frazer BM. Anesthetic doses blocking adrenergic (stress) and cardiovascular responses to incision–MAC BAR. Anesthesiology 1981;54:390–8.

18. Kotrly KJ, Ebert TJ, Vucins E, Igler FO, Barney JA, Kampine JP. Baroreceptor reflex control of heart rate during isoflurane anesthesia in humans. Anesthesiology 1984;60:173–9.

19. Philbin DM, Moss J, Akins CW, et al. The use of $H_1$ and $H_2$ histamine antagonists with morphine anesthesia: a double-blind study. Anesthesiology 1981;55:292–6.

20. Tsay Y-G, Jones R, Calenoff E, et al. A preoperative chymopapain sensitivity test for chemonucleolysis candidates. Spine 1984;9:764–8.

21. Bernstein DI, Gallagher JS, Bernstein IL, Prospective evaluation of chymopapain sensitivity in patients undergoing chemonucleolysis. J Allergy Clin Immunol 1984;73 (suppl):180 (abstr 285).

22. Agre K, Wilson RW, Brim M, McDermott DJ. Chymodiactin: post-marketing surveillance demographic and adverse experience in 29,075 patients. Spine, in press.

23. Bielory L, Kaliner M. Anaphylactoid reactions to radio contrast media. In: Anaphylactoid reactions in anesthesia. International Anesthesiology Clinics, Boston; Little Brown in press.

24. Ring J, Rothenberger K, Clauss W. Combined histamine $H_1$-$H_2$-receptor antagonist pretreatment for prophylaxis of anaphylactoid reactions due to radiographic contrast media (RCM). J Allergy Clin Immunol 1984;73 (suppl):165 (abstr 225).

25. Greenberger P, Patterson R, Kelly J, Stevenson DD, Simon R, Lieberman P. Administration of radiographic contrast media in high-risk patients. Invest Radiol 1980;15 (suppl):S40–3.

ANESTH ANALG
1985;64:1202–4

# Verapamil Does Not Alter Succinylcholine-Induced Increases in Serum Potassium during Halothane Anesthesia in Normal Dogs

Jeffrey L. Roth, MD, Michael Nugent, MD, and Gerald A. Gronert, MD

ROTH JL, NUGENT M, GRONERT GA. Verapamil does not alter succinylcholine-induced increases in serum potassium during halothane anesthesia in normal dogs. Anesth Analg 1985;64:1202–4.

*Six dogs were studied to determine whether verapamil pretreatment exacerbates the increase in serum potassium levels associated with succinylcholine. Dogs were anesthetized with halothane, 1.26 ± 0% (mean ± SEM; end tidal). Arterial blood–gas tensions, blood pressure, heart rate, temperature, and serum potassium levels were measured. Each dog underwent control and experimental studies separated by seven days. In the experimental study, a 0.15 mg/kg bolus of verapamil was followed by a 4.0 μg·kg$^{-1}$·min$^{-1}$ continuous infusion of verapamil. Normal saline was used in the control study. Succinylcholine, 1 mg/kg bolus, was given 10 min after the initial saline or verapamil bolus. Vital signs again were measured 1, 3, 5, 10, and 15 min after succinylcholine, and plasma verapamil levels were measured 8 and 15 min after verapamil administration. Serum potassium concentrations increased from 3.9 ± 0.2 to 5.0 ± 0.2 mEq/L in control studies and from 3.7 ± 0.2 to 4.8 ± 0.3 mEq/L in animals pretreated with verapamil. Verapamil pretreatment does not alter the increase in serum potassium induced by succinylcholine in normal dogs.*

Key Words: HEART—antiarrhythmia agents, verapamil. NEUROMUSCULAR RELAXANTS—succinylcholine. IONS—potassium.

Recently, McCammon and Stoelting (1) demonstrated that propranolol-induced β-blockade exaggerates the increase in serum potassium after succinylcholine administration in the dog. Verapamil (2) or β-blockers (3,4) exacerbate the increases in serum potassium after acute potassium loading. Saltzman et al. (5) have demonstrated that verapamil, when combined with dantrolene, results in hyperkalemia and cardiovascular collapse in normal swine in the absence of exogenous potassium administration. These drugs may therefore unexpectedly alter potassium levels in situations that previously have been considered benign. The purpose of this study was to determine whether verapamil pretreatment, similar to β-blocker pretreatment, increases the elevation of serum potassium induced by the administration of succinylcholine.

## Methods

Six mongrel dogs weighing 13.7 ± 0.5 kg (mean ± SEM) underwent control and experimental studies separated by seven days. In three dogs the control study preceded the experimental study; the order was reversed in the remaining three animals.

Anesthesia was induced with halothane in a canine induction box. After tracheal intubation, $Pa_{CO_2}$ was maintained at 35 ± 0.5 mm Hg prior to succinylcholine administration using a Harvard animal ventilator, and thereafter settings of the ventilator were unchanged. A mixture of $N_2$ and $O_2$ maintained $Pa_{O_2}$ between 120 and 200 mm Hg. Venous and femoral arterial catheters were placed percutaneously. End-tidal halothane was 1.26 ± 0% (mean ± SEM; Beckman LB-2 analyzer, Fullerton, CA). Esophageal temperature was maintained at 37.5 ± 0°C with infrared lamps. Blood–gas tensions, temperature, arterial blood pressure, heart rate, and serum potassium (Flame Photometer) were measured when end-tidal halothane concentrations were stable at 1.25%. In experimental studies, dogs were given a bolus of verapamil, 0.15 mg/kg intravenously, diluted to 10 ml with normal saline and then a verapamil infusion at a rate of 4 μg·kg$^{-1}$·min$^{-1}$ (2). Control dogs received saline only. Eight minutes after the verapamil or saline, laboratory values and vital signs were repeated. Two minutes later, succinylcholine, 1 mg/kg intravenous bolus, was administered. Hemodynamic and laboratory determinations were then repeated 1, 3, 5, 10, and 15 min

---

Supported in part by research grant GM 21729 from the National Institutes of Health, Public Health Service.

Received from the Department of Anesthesiology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. Accepted for publication June 3, 1985.

Address correspondence to Dr. Nugent, Department of Anesthesiology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905.

© 1985 by the International Anesthesia Research Society

after succinylcholine administration. Plasma levels of verapamil were measured 8 and 15 min after verapamil administration and were analyzed by the method of Harapat and Kates (6), as modified by Nugent et al. (2). Statistical analysis utilized paired and unpaired Student's $t$-tests for comparisons within and between groups, respectively, with $P < 0.05$ considered significant.

## Results

Control and verapamil-pretreated dogs had similar increases in serum potassium levels after receiving intravenous succinylcholine, with the largest increase 3 min after succinylcholine administration (Table 1). In the controls, serum potassium increased from 3.9 ± 0.2 to 5.0 ± 0.2 mEq/L; a similar increase in serum potassium was seen in verapamil-pretreated dogs (3.7 ± 0.2 mEq/L to 4.8 ± 0.3 mEq/L).

$Pa\text{CO}_2$ increased 4 mm Hg in both groups and remained elevated throughout the 15-min experimental period after succinylcholine administration. Plasma verapamil levels 8 and 15 min after administration of the verapamil bolus were 90.4 ± 12.1 ng/ml and 62.2 ± 13.9 ng/ml, respectively. Temperature, heart rate, and arterial $P\text{O}_2$ remained stable (Table 1).

## Discussion

Verapamil does not exaggerate the increase in serum potassium that accompanies the bolus injection of succinylcholine. We hypothesized that verapamil might increase elevations in serum potassium after succinylcholine administration because verapamil exacerbates the increases in serum potassium after intravenous potassium infusion in dogs (2) and because propranolol exaggerates increases in serum potassium after administration of succinylcholine (1). These drugs have complex effects on potassium metabolism or fluxes, and the effects are not generally predictable. Thus it was important to address the questions concerning effects of verapamil on succinylcholine-induced increases in serum potassium levels.

The increase in serum potassium caused by succinylcholine in control animals (1.1 mEq/L) was approximately twice that reported by McCammon and Stoelting (1). Anesthesia for the dogs in their study was induced with thiopental (15–20 mg/kg); halothane and nitrous oxide then were given. In contrast, in our animals anesthesia was induced with halothane in a canine induction box. List (7) has shown in humans that thiopental attenuates the increase in serum $K^+$ after succinylcholine administration to less than half the increase seen in patients anesthetized with halothane and oxygen or halothane, oxygen, and nitrous oxide. The use of thiopental in McCammon and Stoelting's protocol may account for the smaller elevations in serum potassium seen after succinylcholine administration.

The maximum increase in serum after succinylcholine in β-blocked dogs occurred 60–90 min after succinylcholine administration (1). In our study, we measured potassium levels for only 15 min because previous reports studying elevations in serum potassium after succinylcholine administration had reported peak values before 15 min (8–11). In addition, serum potassium values in β-blocked animals were significantly elevated compared to control dogs 10 and 15 min after succinylcholine administration, even though the peak serum potassium levels occurred later (1). Our protocol would have documented any early elevations in serum potassium, and it is unlikely that later increases occurred.

The finding that verapamil does not affect succinylcholine-induced increases in serum potassium but does exaggerate elevations in serum potassium after intravenous infusion in dogs (2) might be explained

Table 1. Serum $K^+$ Levels, Arterial Blood–Gas Tensions, and Mean Arterial Pressures in Dogs (mean ± SEM)

| | Serum $K^+$ (mEq/L) | | $Pa\text{CO}_2$ (mm Hg) | | Buffer base (mEq/L) | | Mean arterial pressure (mm Hg) | |
|---|---|---|---|---|---|---|---|---|
| | S | S + V | S | S + V | S | S + V | S | S + V |
| Control | 3.9 ± 0.2 | 3.9 ± 0.2 | 36 ± 0 | 36 ± 0 | 43 ± 1 | 43 ± 1 | 93 ± 9 | 86 ± 7 |
| After verapamil | | 3.7 ± 0.2 | | 35 ± 1 | 43 ± 2 | 43 ± 1 | | 77 ± 9 |
| After succinylcholine | | | | | | | | |
| 1 min | 4.7 ± 0.2[a] | 4.4 ± 0.2[a] | 40 ± 2 | 37 ± 1 | 42 ± 1 | 43 ± 1 | 116 ± 12[a,b] | 85 ± 12[b] |
| 3 min | 5.0 ± 0.2[a] | 4.8 ± 0.3[a] | 40 ± 1[a] | 39 ± 1[a] | 42 ± 1 | 43 ± 1 | 107 ± 10[a] | 88 ± 13 |
| 5 min | 4.9 ± 0.2[a] | 4.8 ± 0.3[a] | 41 ± 1[a] | 39 ± 1[a] | 42 ± 2 | 41 ± 1[a] | 97 ± 9 | 81 ± 12 |
| 10 min | 4.8 ± 0.2[a] | 4.8 ± 0.3[a] | 41 ± 2[a] | 39 ± 1[a] | 42 ± 2[a] | 40 ± 1[a] | 91 ± 8 | 72 ± 12 |
| 15 min | 4.6 ± 0.2[a] | 4.7 ± 0.3[a] | 40 ± 2[a] | 39 ± 1[a] | 42 ± 1[a] | 41 ± 1[a] | 88 ± 7 | 71 ± 11 |

Abbreviations: S, control dogs (succinylcholine only); S + V, dogs given succinylcholine after verapamil pretreatment.

[a] Significantly different from control (paired $t$, $P < 0.05$).

[b] Significantly different (S vs S + V).

partially by the prolonged infusion of large amounts of intravenous KCl (0.075 mEq·kg$^{-1}$·min$^{-1}$) compared to a sudden small efflux of potassium released after a bolus of succinylcholine. The increase in serum potassium after 10 min of KCl infusion was 2.3 ± 0.2 mEq/L compared to an increase of 1.1 mEq/L after succinylcholine administration during the present study.

A major protective mechanism during hyperkalemia consists of the movement of extracellular potassium into the large intracellular pool (12). Larger quantities of potassium may be needed before the effects of verapamil on potassium uptake, distribution, and storage are reflected in serum potassium levels. Further studies examining potassium distribution to various tissues with and without verapamil pretreatment may better explain the difference in these studies. It may be that in circumstances where succinylcholine results in larger serum potassium elevations (e.g., denervated muscle, burns, infection) (9–11), the increase in serum potassium may be greater after verapamil pretreatment. However, succinylcholine would always be contraindicated in this group of patients.

In dogs anesthetized with thiopental, verapamil levels similar to those reported in our study prolong the atrial His bundle conduction time and abolish ventriculoatrial conduction without causing a significant change in sinus rate, cardiac output, left ventricular *dp/dt*, or systemic vascular resistance (13). A dose of verapamil similar to ours resulted in decreases of mean arterial pressure and left ventricular *dp/dt* (14) in halothane-anesthetized dogs (0.93% halothane plus 0.2 mg/kg verapamil). Therefore, higher doses of verapamil were not used in this study. Eight minutes after verapamil, three of our study animals had mean arterial pressures of 70, 66, and 48 mm Hg, and they very likely would have tolerated higher doses of verapamil poorly.

After the succinylcholine bolus in both the verapamil-pretreated and control dogs, small increases in $Pa_{CO_2}$, similar to that described by Hagan et al. (15), were observed for the experimental period. This increase in $Pa_{CO_2}$ is probably secondary to the increased metabolism seen with muscle fasciculations and has little clinical significance.

The authors conclude that verapamil has no effect on the increase in serum potassium induced by succinylcholine administration in normal dogs and is unlikely to have adverse effects on serum potassium in a similar clinical situation.

## References

1. McCammon RL, Stoelting RK. Exaggerated increase in serum potassium following succinylcholine in dogs with beta blockade. Anesthesiology 1984;61:723–5.
2. Nugent M, Tinker JH, Moyer TP. Verapamil worsens rate of development and hemodynamic effects of acute hyperkalemia in halothane-anesthetized dogs: effects of calcium therapy. Anesthesiology 1984;60:435–9.
3. Rosa RM, Silva P, Young JB, Landsberg L, Brown RS, Rowe JW, Epstein FH. Adrenergic modulation of extrarenal potassium disposal. N Engl J Med 1980;302:431–4.
4. Carlsson E, Fellenius E, Lundberg P, Svensson L. $\beta$-adrenergic blockers, plasma potassium, and exercise. Lancet 1978;2:424–5.
5. Saltzman LS, Kates RA, Corke BC, Norfleet EA, Heath KR. Hyperkalemia and cardiovascular collapse after verapamil and dantrolene administration in swine. Anesth Analg 1984;63:473–8.
6. Harapat SR, Kates RE. Rapid high-pressure liquid chromatographic analysis of verapamil. II. Simultaneous quantitation of verapamil and its active metabolite, norverapamil. J Chromatogr 1980;181:484–9.
7. List WF. Serum potassium changes during induction of anaesthesia. Br J Anaesth 1967;39:480–4.
8. Famewo CE. Influence of fazadinium on the potassium efflux produced by succinylcholine. Canad Anaesth Soc J 1981;28:463–6.
9. Kahn TZ, Kahn RM. Changes in serum potassium following succinylcholine in patients with infections. Anesth Analg 1983;62:327–31.
10. Cooperman LH, Strobel GE Jr, Kennell EM. Massive hyperkalemia after administration of succinylcholine. Anesthesiology 1970;32:161–4.
11. Iwatsuku N, Kuroda N, Amaha K, Iwatsuki K. Succinylcholine-induced hyperkalemia in patients with ruptured cerebral aneurysms. Anesthesiology 1980;53:64–7.
12. Kunis CL, Lowenstein J. The emergency treatment of hyperkalemia. Med Clin North Am 1981;65:165–76.
13. Mangiardi LM, Hariman RJ, McAllister RG, Bhargava V, Surawicz B, Shabetai R. Electrophysiologic and hemodynamic effects of verapamil correlation with plasma drug concentrations. Circulation 1978;57:366–72.
14. Kapur PA, Flacke WE. Epinephrine-induced arrhythmias and cardiovascular function after verapamil during halothane anesthesia in the dog. Anesthesiology 1981;55:218–25.
15. Hagan CH, Marshall WK, Weber DM, Snider MT. Succinylcholine increases $CO_2$: neuroanesthetic implications. Anesthesiology 1983;59:A303.

ANESTH ANALG 1985;64:1205–7

## Clinical Reports

# Potential Hazards of Transcatheter Serial Epidural Phenol Neurolysis

Dennis W. Coombs, MD

Epidural neurolysis has been suggested for control of terminal pain due to malignancy (1), including recent use of serial daily phenol injections via a percutaneously placed epidural catheter (2). Racz et al. emphasized the use of a Racz (Arrow International Inc., Reading, PA) epidural catheter with an implanted coiled wire that was fluoroscopically advanced epidurally. This same catheter was then gradually withdrawn allowing small serial daily phenol injections along the neuraxis. The present case report describes a structural disruption that occurred in the epidural portion of a Racz catheter after implantation for phenol neurolysis. Fortunately, adequate analgesia followed the initial phenol injection, even though serial injections were planned. Catheter disruption was discovered fortuitously after removal of the catheter before any further injections were performed. Based upon our experience and previous difficulties with Racz catheters (3), a modification in the technique of serial phenol injections or return to separate percutaneous epidural phenol injections is suggested.

## Case Report

A 50-yr-old man was referred in August 1984 for treatment of bilateral chest pain secondary to a rapidly progressive, poorly differentiated carcinoma of the lung. For two months he had been treated with escalating narcotic medications, with poor control of his chest wall pain. In September 1984, because 840 mg of intramuscular morphine equivalents per day (total systemic narcotic intake expressed in equivalent amount of morphine after Houde (4)) still left him largely bedridden and frequently confused or disoriented, intrathecal morphine was initiated using an implanted infusion pump (5). After initial success, he developed tolerance to intrathecal morphine and was readmitted to the hospital for pain control. The primary complaint was bilateral chest pain, probably because of partial T5 collapse, but the major component involved the right chest wall in a T4–8 distribution. He was now preterminal and bedridden with extreme inanition; the right lung was largely collapsed due to tumor. He was alternately either somnolent or crying out in pain on a regimen of up to 70 mg intravenously of morphine/day. Thus serial thoracic epidural phenol neurolysis was elected (2). It was hoped that this would control his pain and allow a short narcotic-free holiday during which improved cognitive interaction with his family could occur.

In October 1984, neurolysis was performed. The patient was placed in the right lateral decubitus position under light thiopental and nitrous oxide sedation and 17-gauge Tuohy needle was used to identify the thoracic epidural space at T8–9 by the loss-of-resistance technique. A 20-gauge Racz epidural catheter was then passed and fluoroscopically guided 10–11 cm rostrally to T5–6 where an obstruction was encountered. As shown in Figure 1, a thoracic epidurogram was performed with 8 ml of metrizamide (Amipaque, Winthrop Breon Laboratories, NY, NY; 200 mg/ml) to verify epidural catheter position. Peculiarly, an initial circular area of contrast pooling occurred at T8 opposite the catheter entrance along with epidural outlining of the spinal canal. Three and one-half ml of 10% phenol suspended in a 50% glycerin and saline solution was then injected using

---

These observations were made during a study supported in part by NCI Grant No. CA 33865-01.

Received from the Norris Cotton Cancer Center and Dartmouth-Hitchcock Medical Center, Hanover, New Hampshire. Accepted for publication June 7, 1985.

Address correspondence to Dr. Coombs, Department of Surgery, Section of Anesthesiology, Dartmouth-Hitchcock Medical Center, 2 Maynard Street, Hanover, NH 03756.

© 1985 by the International Anesthesia Research Society

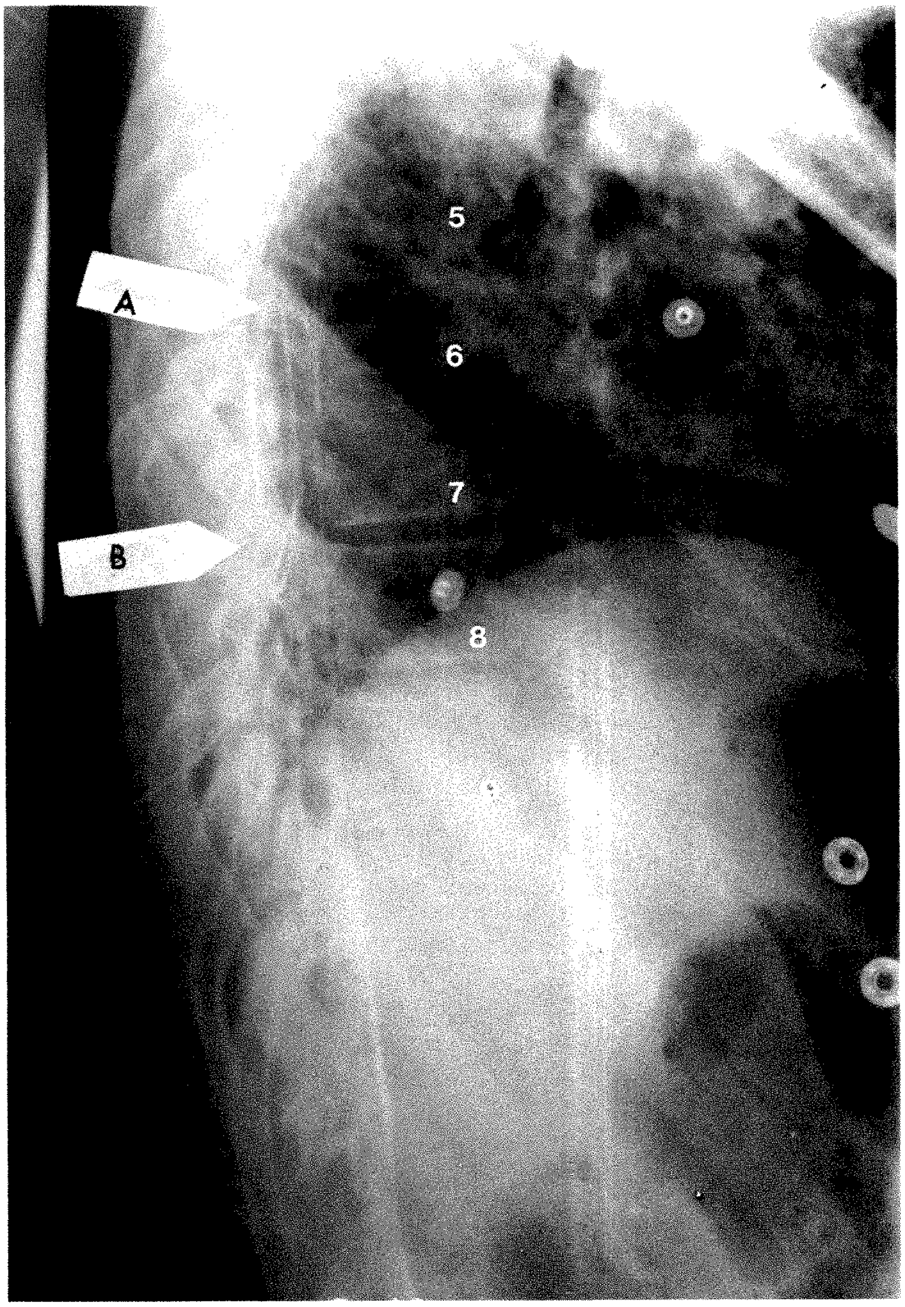


Figure 1. Metrizamide epidurogram via T8-9 epidural catheter. *Arrow A* indicates epidural catheter tip; the partial T5 collapse is poorly visualized. *Arrow B,* initial contrast density appeared 1–2 cm rostral to catheter epidural entrance and correlated well with the point of disruption 8 cm from the tip.

a tuberculin syringe. The catheter was taped in place in anticipation of a second injection after 24 hr. Forty-eight hours later, the patient was still almost pain-free; so the catheter was removed. Inspection revealed nearly complete circumferential disruption of the catheter 8 cm from its tip. Injection of saline was performed, revealing fluid egress at the site of disruption coincident with the site of early metrizamide pooling. The patient was discharged home on 40 mg oral morphine equivalents per day without apparent sequelae.

## Discussion

That pain control occurred in this case without untoward sequelae is fortunate. The neurolytic technique of Racz et al. is based upon daily serial injections of phenol with progressive withdrawal of the catheter producing distribution of phenol to progressively more caudal dorsal roots (2). In theory, this avoids large-volume injections that might be disastrous if inadvertent intrathecal injection occurred. The technique also minimizes the number of needle replacements, reducing manipulation of sick fragile patients. Disruption of this epidural catheter might, if followed by incremental withdrawal and repeat injections, have had several adverse consequences. Most obvious is complete breakage of the catheter, leaving an epidural foreign body. This is perhaps of questionable importance given the duration of expected survival; however, such foreign bodies are a nidus for infection. Associated pressure or irritation from a catheter fragment impinging upon a nerve root might yield difficult-to-treat pain. Of more practical significance, proximal disruption of the catheter might lead to injection at a more caudal level than expected. This could have variable consequences, ranging from absence of pain relief to injury of nerve roots outside the distribution of pain. Similarly, injection into soft tissue outside the spinal canal could result in extensive tissue necrosis, cutaneous fistula, or sterile abscess formation. Less likely but still imaginable is the risk that disruption of the catheter might result in the distal fragment puncturing the dura to produce a cerebrospinal fluid leak or an avenue for direct but unexpected intrathecal neurolytic instillation.

Disruption of the Racz epidural catheter is not an isolated occurrence in our experience. This is the fourth defect encountered at this institution though only the first associated with epidural neurolysis. The other Racz catheter defects included the following: 1) two catheters in use for obstetrical analgesia that cracked and leaked at the junction of plastic connector hub and catheter; 2) a chronic epidural catheter that began to leak on the third day of bupivicaine infusion for cancer pain analgesia—a catheter defect was found a few mm deep to the skin entrance site with an associated superficial subcutaneous infection; and 3) an obstetrical analgesic catheter in use for 10 hr that developed leaks at the skin entrance site and midway between hub and skin. Lingenfelter described a different type of problem with this catheter design (3). He encountered difficulty removing four epidural catheters; one Racz catheter unravelled on withdrawal, though without apparent disruption of the catheter wall.

Potential etiologies for catheter failure include trauma from the Tuohy needle, twisting or kinking, high pressure injection with or without a defect in the catheter wall, defective manufacturing or inherently brittle catheter materials. In the present case catheter introduction was unremarkable except for obstruction to advancement encountered at T5–6. As seen in Figure 1, the catheter looped on advancement. Notably, the Tuohy needle was pulled back to avoid catheter shearing. Subsequent metrizamide injection obscured visualization of the loop as the catheter was retracted, thus an unrecognized kink might have occurred. The pressure required to inject phenol or metrizamide was not unusually high, making pressure induced catheter blowout less likely. The author tested several Racz catheters for stability when exposed to phenol. Five days of exposure to a 10% phenol and saline solution had no perceptible effect on the catheter wall. Recent discussions with a representative of the manufacturer indicates disruption has been reported to the manufacturer from other institutions as well, though most commonly when 18-gauge Tuohy needles are used for introduction (personal communication, PL Frankhouser, Marketing Manager, Arrow International Inc., Reading, PA).

Catheter breakage with complete separation of the two ends might be detected on a spine x-ray or fluoroscopy without contrast injection, however, incomplete breakage without a discontinuity could easily be missed without radiographic contrast injections. Short of repeating metrizamide epidurography with its attendant risks, i.e., major motor seizures, aseptic meningitis, CNS irritation, and the requirement for special rooms and equipment, little can be done to absolutely assure catheter integrity and position. Perhaps a test injection of local anesthetic solution revealing a segmental epidural block is required before repeating phenol injection when using this serial injection technique. Otherwise daily repeat epidural needle placements would be preferable even though associated with obvious inconvenience and even suffering in these patients. In conclusion, caution should be exercised when repeated neurolytic injections are planned using indwelling epidural catheters designed for serial epidural injections.

The author gratefully acknowledges Lawrence Jenson, RN, and Carol Murphy, RN for their help with these patients; George Kinsman, OT, for excellent operative support; and Kristin Lanphear and Sue Schott for manuscript preparation and editing.

## References

1. Bromage PR. Epidural analgesia. Philadelphia, PA: W.B. Saunders, 1978:626–36.
2. Racz GB, Sabonghy M, Gintaitas J, Kline WM. Intractable pain therapy using a new epidural catheter. JAMA 1982;248:579–81.
3. Lingenfelter RW. Hazard of a new epidural catheter. Anesthesiology 1983;58:292–3.
4. Houde RW. Systemic analgesics and related drugs: narcotic analgesics. In: Bonica JJ, Ventafridda V (eds). Advances in pain research and therapy, vol. 2. New York, NY: Raven, 1979:263–73.
5. Coombs DW, Saunders RL, Gaylor MS, Block AR, Colton T, Harbaugh R, Pageau MG, Mroz W. Relief of continuous chronic pain by intraspinal narcotics infusion via an implanted reservoir. JAMA 1983;250:2336–9.

1208 ANESTH ANALG
1985;64:1208–10

# Bedside Diagnosis of Bilateral Diaphragmatic Paralysis in a Ventilator-Dependent Patient after Open-Heart Surgery

Karen A. Brown, MD, V. Hoffstein, MD, FRCP(C), and Robert J. Byrick, MD, FRCP(C)

Respiratory failure is an infrequent complication after open-heart surgery, particularly in the absence of significant preoperative lung pathology. This report describes a patient who remained ventilator-dependent for nine weeks after aortic valve replacement and coronary artery bypass surgery with bilateral diaphragmatic paralysis.

## Case Report

A 62-yr-old man (93.5 kg; 190 cm) was admitted to the hospital with a 6-month history of decreasing exercise tolerance. He had smoked only two cigarettes per day for many years and had no clinical evidence of chronic bronchitis or emphysema. Preoperative cardiac catheterization demonstrated an aortic valve gradient of 93 mm Hg, 3+ aortic regurgitation, and a left ventricular pressure of 250/19 mm Hg. The cardiac index was 2.97 $L{\cdot}min^{-1}{\cdot}m^2$. He underwent elective aortic valve replacement and insertion of a single left anterior descending coronary artery bypass graft.

His intraoperative course was uncomplicated. Aortic cross-clamp time was 111 min. Myocardial preservation was maintained with crystalloid cardioplegia, external cold slush, and the Boncheck-Shiley Cardiac jacket (BCJ 401). This jacket was bathed in a 50:50 mixture of 75% alcohol and water as suggested in the manufacturer's instructions to cool the bath temperature below 4°C. The lowest recorded myocardial septal temperature was 10°C.

On the first postoperative day, attempted weaning from ventilatory support using intermittent mandatory ventilation (IMV) ended prematurely with self-extubation. Within several hours tachypnea and respiratory distress necessitated reintubation and ventilation. Over the subsequent nine weeks his maximum inspiratory pressure ranged from −13 to −15 cm $H_2O$, and forced vital capacity varied from 300 ml to 500 ml in the semi-upright position and from 150 to 300 ml in the supine position.

On day 4 he was noted to have paradoxical abdominal movement on inspiration. That is, when removed from assist-control ventilation and asked to breathe in the supine position, the ventral abdominal wall moved inward on inspiration.

Fluoroscopy of both diaphragms in the supine position during spontaneous ventilation, while intubated, showed an immobile left hemidiaphragm. The right hemidiaphragm moved cephalad on expiration and caudad on inspiration.

Transdiaphragmatic pressure tracings were recorded during spontaneous breathing in the semirecumbent position. Esophageal pressure was measured with a 10-cm latex balloon positioned in the esophagus 36 cm from nares and 10 cm proximal to the esophago-gastric junction. Gastric pressure was measured using a similar balloon catheter assembly in the stomach positioned 60 cm from the nares. The placement of both balloons was confirmed radiographically. Simultaneous tracings were made with a Validyne transducer (Model MP 45-4).

Figure 1 shows a tracing of esophageal (Pes) and gastric (Pg) pressures. Note that baseline pressures are different because the Pes at functional residual capacity is determined by lung recoil, whereas Pg is determined by the total weight of the abdominal contents. Normally during spontaneous ventilation Pes and Pg fluctuate in opposite directions (i.e., on inspiration Pes becomes more negative while the gastric pressure becomes more positive) (1). The baseline values of esophageal pressures as well as the magnitude of pressure changes during breathing will depend, among other things, on the position of the patient. However, the direction of pressure changes (i.e., inspiratory increase in gastric pressure and decrease in esophageal pressure) is preserved independently of posture. In fact, because in the supine position the main contribution to tidal volume comes from the

---

Received from the Departments of Anesthesia and Medicine, St. Michael's Hospital, Toronto, Canada. Accepted for publication June 10, 1985.

Address correspondence to Dr. Byrick, Dept. of Anaesthesia, St. Michael's Hospital, 30 Bond Street, Toronto, ON M5B 1W8, Canada.

© 1985 by the International Anesthesia Research Society

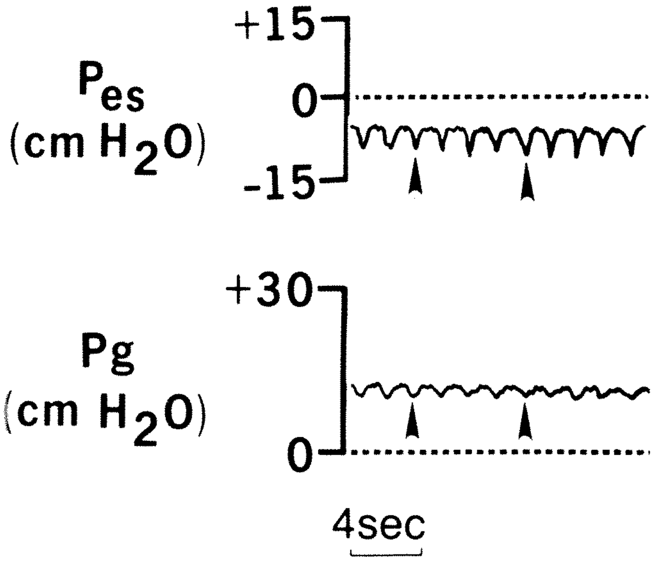


Figure 1. Recordings of esophageal pressure (Pes) and gastric pressure (Pg). Arrows indicate in-phase simultaneous breaths. See text for further explanation.

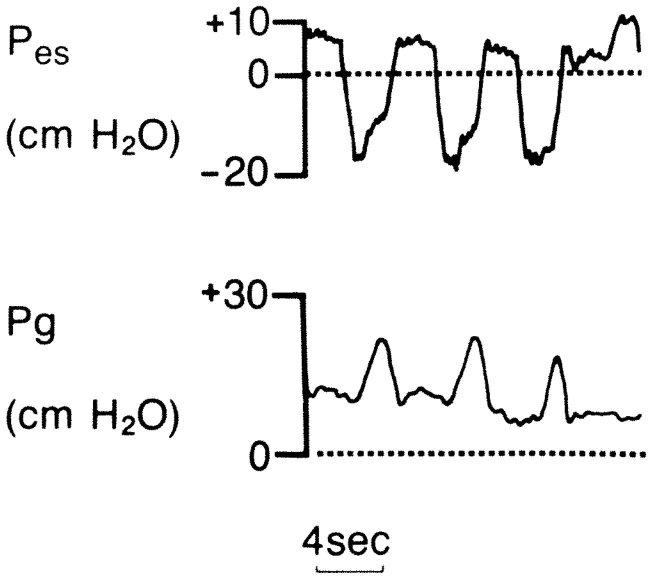


Figure 2. Recordings of simultaneous esophageal pressure (Pes) and gastric pressure (Pg). See text for further explanation.

diaphragm rather than from the intercostal muscles, we would expect a strongly positive gastric pressure deflection on inspiration. Figure 1 demonstrates that in this patient, during inspiration (denoted by arrows) both Pes and Pg showed an in-phase negative deflection, consistent with the diagnosis of bilateral diaphragmatic paralysis.

A tracheostomy was performed on day 24. By week 8 his maximum inspiratory pressure was $-25$ cm $H_2O$ and his upright forced vital capacity was 900 ml. He was successfully weaned from ventilator support over the subsequent week, and discharged from ICU.

A transdiaphragmatic pressure study was performed 8 months postoperatively with the patient in a similar semi-recumbent position. The result is shown in Figure 2. The inspiratory fluctuations are out of phase, consistent with the recovery of diaphragmatic function.

## Discussion

The diagnosis of bilateral diaphragmatic paralysis can be difficult and requires a high degree of clinical suspicion, especially in a ventilator-dependent patient.

The most important clinical signs are paradoxical abdominal wall motion and postural orthopnea. Four laboratory tests have been used to make the diagnosis: 1) fluoroscopy, 2) spirometry, 3) phrenic nerve conduction studies, and 4) transdiaphragmatic pressure studies.

There are many reports in the literature stressing the fact that fluoroscopy may be misleading in bilateral diaphragmatic paralysis (2–4). Loh et al. (5) offered a mechanical explanation for the imprecision of fluoroscopy as a diagnostic tool, because expiration can be active, forcing the flaccid diaphragm cephalad so that it appears to descend on inspiration.

Complex spirometry is often impossible in a ventilated patient, but a simple vital capacity (VC) can be measured easily. A consistent decrease in VC when moving from the sitting to supine posture supports the diagnosis of bilateral diaphragmatic paralysis.

Markand et al. (6) utilized phrenic nerve conduction studies in patients undergoing open-heart surgery and found an 11% incidence of phrenic nerve damage and a 1.5% incidence of phrenic nerve paralysis. We attempted to measure phrenic nerve conduction in our patient, however, mechanical difficulties with equipment made interpretation of results inconclusive.

A transdiaphragmatic pressure study in ventilator-dependent patients is particularly valuable, as it is easily measured at the bedside. Placement of the esophageal and gastric catheters is no more stressful to a patient than passing a nasogastric tube. The absolute transdiaphragmatic pressure, which may be influenced by lung volume, patient position, and catheter placement (7), is not required. Rather it is the qualitative in-phase deflections of the esophageal and gastric pressures with voluntary respiration (Figs. 1,2) that suggest the diagnosis. This is not to say that an in-phase esophageal gastric pressure trace is pathognomonic of bilateral diaphragmatic paralysis. Macklem (8) has shown that healthy untrained volunteers may also exhibit this pattern. But in the appropriate clinical situation an abnormal tracing may point to the cause of refractory respiratory failure.

Myocardial preservation techniques have been implicated as a cause of bilateral diaphragmatic paralysis after cardiac surgery (2,3). Scannel (9) coined the term "frost-bitten phrenic" in 1963. In 1976 Marco et al. (10) used a dog model and applied ice chips to the intrapericardial segment of the left phrenic nerve for 30–60 min, thus abolishing phrenic nerve activity to electrical stimulation for 25–52 days.

We speculate, on the basis of the transdiaphragmatic pressure studies and the spirometric changes with posture, that our patient had bilateral diaphragmatic paralysis from intraoperative cold injury to the phrenic nerves. We suspect that cold injury resulted from a combination of a long aortic cross-clamp time, traction on the pericardial portion of the nerve, topical cold slush, and the alcohol:water cooling bath for the Bonchek–Shiley Cardiac jacket. Although myocardial preservation is essential, excessive cooling of the heart may impose a risk of cold injury to the intrapericardial segment of the phrenic nerves. Until further studies become available, we will cool the Boncheck–Shiley jacket in saline alone and not an alcohol–saline bath.

Lastly, we echo Chandler's comment that "the frost bitten phrenic" will recover (3). Recovery of diaphragmatic function can be monitored at the bedside using transdiaphragmatic pressure studies.

We thank Robert Taylor for technical assistance, Susan Lamb for the artwork, and Patricia Slusarenko for typing the manuscript.

## References

1. Milic-Emili J, Mead J, Tunner J, Glauser E. Improved technique for estimating pleural pressure from esophageal balloons. J Appl Physiol 1964;19:217–23.
2. Kohorst W, Schonfeld S, Altman M. Bilateral diaphragmatic paralysis following topical cardiac hypothermia. Chest 1984;85:65–8.
3. Chandler K, Rozas C, Kory R, Goldman A. Bilateral diaphragmatic paralysis complicating local cardiac hypothermia during open heart surgery. Am J Med 1984;77:243–9.
4. Schiavi E. Isolated bilateral diaphragmatic paresis with interstitial lung disease. Am Rev Resp Dis 1984;129:337–9.
5. Loh L, Goldman M, Newsom Davis J. The assessment of diaphragm function. Medicine 1977;56:165–9.
6. Markand OM, Moorthy SS, Mahomed Y, King R, Brown JW. Postoperative phrenic nerve palsy in patients with open heart surgery. Ann Thorac Surg 1985;39:68–73.
7. DeTroyer A, Estenne M. Limitations of measurement of transdiaphragmatic pressure in detecting diaphragmatic weakness. Thorax 1981;36:169–74.
8. Macklem P, Gross P, Grassino A, Roussos C. Partitioning of inspiratory pressure swings between diaphragm and intercostal accessory muscles. J Appl Physiol 1978;44:200–8.
9. Scannel J. Results of open-heart operation for acquired aortic valve disease. J Thorac Cardiovasc Surg 1963;45:64–8.
10. Marco J, Hahn J, Barner H. Topical cardiac hypothermia and phrenic nerve injury. Ann Thorac Surg 1977;23:235–7.

ANESTH ANALG 1211
1985;64:1211-3

# The Effect of Intravenous Lidocaine on the Increase in Intraocular Pressure Induced by Tracheal Intubation

Benjamin Drenger, MD, Jacob Pe'er, MD, David BenEzra, MD, PhD, Ruth Katzenelson, MD, and Joseph T. Davidson, MD, FFARCS

An increase in intraocular pressure (IOP) is observed during and after laryngoscopy and tracheal intubation (1,2). Brief elevation of IOP is of little consequence in normal or even glaucomatous eyes, as long as the eyeball is intact (1). However, in a patient with an ocular laceration, perforation, or recent surgical ocular intervention, even a transient increase in IOP may be hazardous (1,3). Although a small dose of a nondepolarizing agent such as gallamine or *d*-tubocurarine given before succinylcholine attenuates the elevation of IOP caused by succinylcholine (4), there is an additional and more significant increase caused by tracheal intubation itself (1,2).

During induction of anesthesia, intravenous lidocaine reduces the autonomic responses to laryngoscopy and intubation (5,6), and acts as an effective cough suppressant (7). We evaluated the influence of intravenous lidocaine on the changes in IOP after tracheal intubation.

## Materials and Methods

Forty healthy children (ASA class I), 19 boys and 21 girls, undergoing general anesthesia for strabismus, ptosis, or lacrimal system surgery were studied. They ranged in age from 1 to 10 yr and weighed between 10 and 30 kg. Children weighing up to 15 kg were premedicated with a suppository containing a mixture of 250 mg thiopental, 3.5 mg of Pantopon, and 0.17 mg of scopolamine. Those weighing more than 15 kg received twice this dose.

Anesthesia was induced by inhalation of nitrous oxide–oxygen (2:1), with the gradual addition of halothane, up to 2%. After central fixation of the pupils, an intravenous catheter was inserted. Five minutes after induction of anesthesia, baseline measurements of IOP were recorded and each child received, in a double-blind randomized manner, an intravenous injection of 0.13 ml/kg of a coded solution prepared by a qualified pharmacist, containing either 1.5% lidocaine HCl without preservative, 2 mg/kg, or normal saline. IOP was recorded 1 and 2 min later. The trachea was intubated using a noncuffed tube as soon as the jaw muscles were well relaxed. This was approximately 7 min after commencement of induction and 2 min after the intravenous injection of the drug. Muscle relaxants were not used, and in all cases the intubation was smooth and uneventful. The IOP was measured immediately after intubation and again 1, 2, 3, and 4 min later. The IOP was measured in both eyes with a Schiotz tonometer. The mean values obtained from the IOP measurements of all the children in the group were statistically evaluated using the Student's *t*-test. $P < 0.05$ was taken as indicating significance.

## Results

Twenty-one children received intravenous injections of saline, and 19 children received lidocaine. The mean age and weight of those in the saline and lidocaine groups were 5.6 ± 0.7 (SEM) and 5.2 ± 0.7 (SEM) yr and 20.3 ± 1.7 (SEM) and 19.3 ± 1.8 (SEM) kg, respectively. The IOP of both eyes in the control and in the lidocaine groups during induction of anesthesia and immediately after the tracheal intubation is presented in Figure 1. The baseline pressure differences between the two eyes were small and within the normal range, as were the changes associated with the induction of anesthesia and intubation.

The baseline values were 12.5 ± 0.5 (SEM) mm Hg and 14.6 ± 0.5 mm Hg in the saline and lidocaine groups, respectively. Two minutes after injection, immediately before intubation, IOP was significantly

---

Received from the Departments of Anesthesiology and Ophthalmology, Hadassah University Hospital, Jerusalem, Israel. Accepted for publication June 14, 1985.

Address correspondence to Dr. Drenger, Department of Anesthesiology, Hadassah University Hospital, PO Box 12000, 91120 Jerusalem, Israel.

© 1985 by the International Anesthesia Research Society

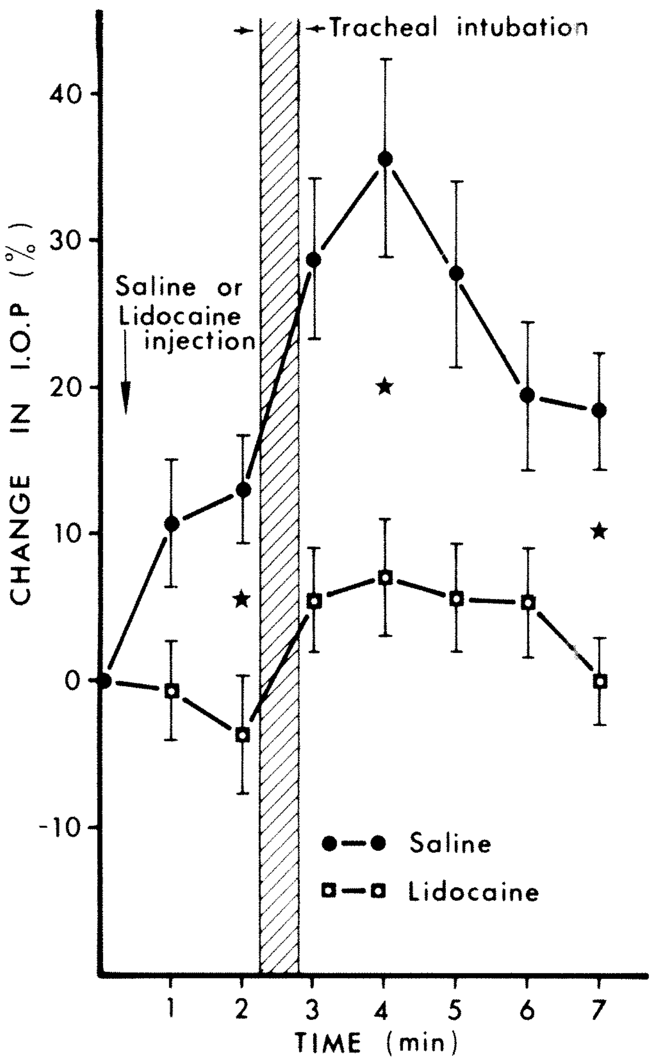


Figure 1. Time course of changes in intraocular pressure (IOP). Points and bars indicate percent change from baseline (mean ± SEM). The initial IOP (time 0) represents the baseline IOP (see text). *$P < 0.001$ (for the difference between maximal IOP in control and lidocaine groups).

lower in patients given lidocaine than in those given saline. One minute after intubation IOP was 16.9 ± 0.9 mm Hg (35.3 ± 7.0% above baseline) in the control group and 15.4 ± 0.6 mm Hg (7.1 ± 4.0% above baseline) in the experimental group. The increase above baseline levels was statistically significant in the saline group ($P < 0.001$), but not in the lidocaine group ($P < 0.2$).

Peak IOP after intubation was 18.0 ± 0.9 mm Hg after saline, a significant 5.5 ± 0.7 mm Hg above baseline levels. Peak IOP after intubation when lidocaine had been given was 16.1 ± 0.2 mm Hg, a lesser but statistically significant 1.5 ± 0.27 mm Hg increase above baseline levels. Peak increases in IOP were statistically significant less ($P < 0.001$) after lidocaine than after saline.

## Discussion

Tracheal intubation increases intraocular pressure (1,2). These short-term changes are probably of little consequence in normal healthy individuals. However, in patients with a lacerated globe (1,3), they may be hazardous.

The increase in IOP is possibly a result of either sympathetically mediated vasoconstriction or an increase in central venous pressure (CVP) associated with coughing, or both. The increase in IOP was significantly less when intravenous lidocaine (2 mg/kg) was given before the tracheal intubation. Analysis of the IOP data of those patients who did not cough in the two groups, showed essentially the same significant difference in IOP, suggesting that the elevation of IOP could be attributed to an autonomic reflex, not to an increase in the CVP caused by coughing.

Some suppression of autonomic and cough reflexes is achieved by the inhibiting action of 2 mg/kg intravenous lidocaine on the polysynaptic spinal reflexes, with no apparent cardiovascular depressant effect (8). Our findings do not indicate the optimal time for tracheal intubation. However, the dosage of lidocaine used produces an effective and safe blood level in the first 5 min (9,10) after intravenous injection. It is likely that the safest time for intubation, from the point of view of IOP stability, is within that time. The peak value of IOP was recorded, in most cases, 1 min after intubation. Clinically, the highest IOP reached is the critical factor irrespective of time, and any reduction in the IOP can alleviate harm in the lacerated eye.

The present results indicate that the use of 2 mg/kg of intravenous lidocaine approximately 2 min before tracheal intubation significantly attenuates the increase in IOP. This procedure is strongly recommended in patients with penetrating eye injuries or recent surgical ocular incisions, and it is particularly helpful when these patients have to be anesthetized by rapid sequence induction because of the danger of aspiration of stomach contents.

## References

1. Joshi C, Bruce DL. Thiopental and succinylcholine: action on intraocular pressure. Anesth Analg 1975;54:471–5.
2. Meyers EF, Krupin T, Johnson M, Zink H. Failure of nondepolarizing neuromuscular blockers to inhibit succinylcholine-induced increased intraocular pressure. A controlled study. Anesthesiology 1978;48:149–51.
3. Duncalf D, Foldes FF. Effect of anesthetic drugs and muscle

relaxants on intraocular pressure. In: Smith RB, ed. Anesthesia in ophthalmology. Boston, MA: Little Brown and Company. International Ophthalmology Clinics, vol 13, no 2, 1973:21–34.

4. Miller RD, Way WL, Hickey RF. Inhibition of succinylcholine-induced increased intraocular pressure by non-depolarizing muscle relaxants. Anesthesiology 1968;29:123–6.
5. Abou-Madi MN, Keszler H, Jacoub JM. Cardiovascular reactions to laryngoscopy and tracheal intubation following small and large intravenous doses of lidocaine. Canad Anaesth Soc J 1977;24:12–9.
6. Hamill JF, Bedford RF, Weaver DC, Colohan AR. Lidocaine before endotracheal intubation: intravenous or laryngotracheal? Anesthesiology 1981;55:578–81.
7. Steinhaus JE, Gaskin L. A study of lidocaine as a suppressant of cough reflex. Anesthesiology 1963;24:285–90.
8. De Jong RH. Physiology and pharmacology of local anesthesia. Springfield, IL: Charles C Thomas, 1970:144–57.
9. Baraka A. Intravenous lidocaine controls extubation laryngospasm in children. Anesth Analg 1978;57:506–7.
10. Gianelly R, Von Der Groeben JO, Spivack AP, Harrison DC. Effect of lidocaine on ventricular arrhythmias in patients with coronary heart disease. N Engl J Med 1967;277:1215–9.

1985;64:1214–6

# Arrhythmias during Venous Cannulation prior to Pulmonary Artery Catheter Insertion

Roger L. Royster, MD, William E. Johnston, MD, Glenn P. Gravlee, MD, Stanley Brauer, MD, and Dan Richards, MD

Previous reports of arrhythmias during pulmonary artery (PA) catheter insertion have not directly assessed the incidence of arrhythmias occurring during the cannulation of the venous system using a flexible guidewire, vessel dilator, and catheter sheath introducer system (1,2). We report a case of a life-threatening ventricular arrhythmia occurring during insertion of a guidewire through the right internal jugular vein, and a prospective clinical study prompted by that case to determine the incidence of arrhythmias during right internal jugular vein cannulation prior to pulmonary artery catheterization.

## Case Report

A hypotensive 69-yr-old woman with a history of myocardial infarction, arrhythmias, and urinary tract infections was admitted to the intensive care unit with a diagnosis of septic shock. Treatment with dopamine and parenteral fluids stabilized the patient's condition, and after appropriate cultures were obtained, antibiotic therapy was begun. On the third day of hospitalization, the patient became oliguric and a pulmonary artery catheter was inserted through the right internal jugular vein. The initial hemodynamic values revealed a cardiac output of 2.6 L/min, a central venous pressure of 20 mm Hg, a PA pressure of 39/25 mm Hg, and PA wedge pressure of 20 mm Hg. Dobutamine was added to the dopamine infusion, but the patient continued to have intermittent episodes of hypotension. Chest roentgenograms showed bilateral pleural effusions and a cardiac silhouette suggesting pericardial effusion, which was confirmed by echocardiography. Pericardiocentesis resulted in marked hemodynamic improvement and yielded purulent fluid with gram-positive cocci.

Despite brief improvement, the patient continued to have marginal hemodynamic stability, poor urine output, and increasing peripheral edema. As a septic precaution, all intravascular catheters were changed. During reinsertion of the PA catheter, guidewire insertion resulted in sustained ventricular tachycardia that degenerated into ventricular fibrillation, which required defibrillation. A bolus injection of lidocaine was given, followed by an intravenous infusion of lidocaine after which the remainder of the catheterization proceeded uneventfully.

## Methods

The study population consisted of 52 stable, adult cardiac surgical patients without previously documented cardiac arrhythmias in whom PA catheters were inserted for elective perioperative monitoring. A history of cardiac arrhythmias or arrhythmias noted by electrocardiographic monitoring prior to catheterization excluded patients from the study. The patients were similar in regard to age, sex, and type of operative procedure (Table 1). All PA catheters were inserted through the right internal jugular vein by experienced anesthesia residents or fellows using an 8.5-French percutaneous sheath introducer kit (Arrow International Inc., Reading, PA) (Fig. 1). Continuous electrocardiographic recording was employed during insertion of the guidewire, the dilator, and introducer sheath, and during removal of the guidewire. In 26 patients (group 1), the residents or fellows used standard techniques and approaches for venous cannulation. In an additional 26 patients (group 2), the resident or fellow inserted the guidewire (44.5 cm long) a short distance into the internal jugular vein, then, using the length of the vessel dilator (20.5 cm) as a reference, advanced the guidewire until the length of wire outside the skin slightly exceeded the length of the dilator (less than 22 cm intravenously). This prevented initial guidewire overinsertion, defined as the necessity to withdraw the wire through the dilator to allow distal control. The dilator and sheath were then

---

Received from the Department of Anesthesia, Wake Forest University Medical Center, Bowman Gray School of Medicine, Winston-Salem, North Carolina. Accepted for publication June 14, 1985.

Address correspondence to Dr. Royster, Department of Anesthesia, Bowman Gray School of Medicine, 300 S. Hawthorne Road, Winston-Salem, NC 27103.

© 1985 by the International Anesthesia Research Society

Table 1. Patient Population

| | Group 1 ($n$ = 26) | Group 2 ($n$ = 26) |
|---|---|---|
| Sex | | |
| Males | 19 | 21 |
| Females | 7 | 5 |
| Age (yr) | 42–71 | 43–69 |
| Operation | | |
| Coronary grafting | 24 | 23 |
| Valve replacement | 2 | 3 |

Table 2. Incidence and Type of Arrhythmias during Guidewire Insertion

| Intravenous guidewire (cm) | Group 1 ($n$ = 26) >22 | Group 2 ($n$ = 26) <22 |
|---|---|---|
| Incidence | 15 (58%)[a] | 4(15%)[a] |
| Type | | |
| PAC | 6 | 3 |
| PAC,PVC | 4 | 1 |
| PVC | | |
| Multifocal | 1 | |
| Bigeminy | 2 | |
| VT | 2 | |

Abbreviations: PAC, premature atrial contraction; PVC, premature ventricular contraction; VT, ventricular tachycardia.

[a] $P < 0.002$ between groups 1 and 2.

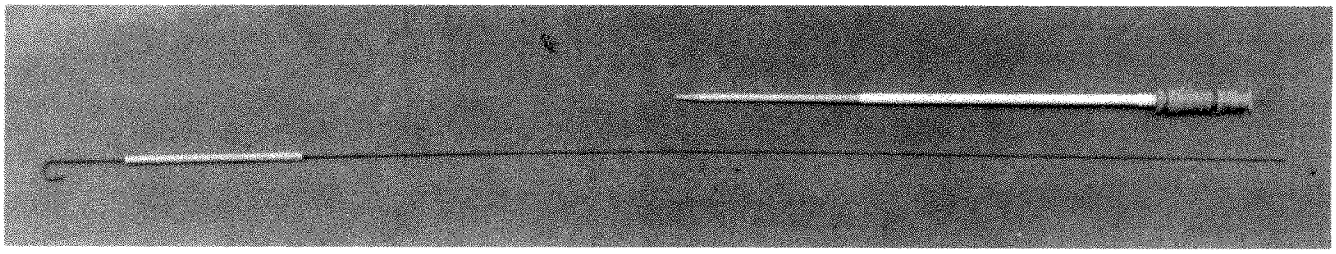


Figure 1. The length of the dilator–sheath introducer, 20.5 cm (top), compared to the length of the guidewire, 44.5 cm (bottom), from a commercially available introducer kit.

placed over the guidewire. Next, the attending anesthesiologist, wearing sterile gloves, secured the guidewire to prevent migration of the wire during advancement of the introducer sheath and dilator unit. The electrocardiographic tracings from the two groups were then examined for arrhythmias. Data were analyzed using $\chi^2$, with a value of $P < 0.05$ considered significant. This study was approved by the Clinical Research Practices Committee.

## Results

The incidence and type of arrhythmias between the two groups are shown in Table 2. All arrhythmias occurred during guidewire insertion or during advancement of the dilator–sheath complex over the guidewire. Fifteen patients (58%) in group 1 ($n$ = 26) developed arrhythmias. Both atrial and ventricular arrhythmias occurred, including more serious ventricular arrhythmias such as bigeminy, multifocal premature ventricular contractions, and ventricular tachycardia (three consecutive premature beats). Only four patients (15%) in group 2 ($n$ = 26) developed arrhythmias. One patient had a premature ventricular contraction; three patients had premature atrial contractions. The incidence of arrhythmias in groups 1 and 2 differed significantly ($P \leq 0.002$). All arrhythmias in both groups converted spontaneously, and none were clinically significant.

## Discussion

Mechanical irritation of the cardiac chambers that commonly induces ectopic activity is abolished by removal of the stimulus (3,4). Prophylactic lidocaine seldom prevents these arrhythmias (3,4). The incidence of ventricular arrhythmias with the direct passage of a PA catheter in critically ill patients varies from 53 to 68% (1,2), with Elliott et al. (1) finding some deviation from baseline rhythm in 77% of patients during catheter insertions. A study of PA catheter insertion prior to cardiac surgery showed an incidence of ventricular arrhythmias of 65% (4). Nonsustained ventricular tachycardia occurs during 18–30% of insertions (1,3,4). Sprung et al. reported a 33% incidence of ventricular tachycardia in critically ill patients during catheterization of the right side of the heart (5). Two patients required antiarrhythmic therapy or precordial thump, and one patient died in ventricular fibrillation.

The Seldinger technique, a popular means of attaining venous access for PA catheter insertion, requires a guidewire, a venous dilator, and introducer sheath. The introducer kit used in this study contains a 44.5-cm guidewire and a 20.5-cm venous dilator (Fig. 1). The guidewire's length is sufficiently long to allow entry into the right ventricle during initial insertion and unintentional advancement as the venous dilator and catheter introducer are passed into the vein. Frequently, as the dilator is threaded over the guidewire, withdrawal of the wire is required to control the distal tip. This indicates overinsertion. When the inserted length of guidewire is not carefully controlled, the incidence of atrial and ventricular arrhythmias is similar to that associated with PA catheterization (1,2). In contrast, when the length of guidewire inserted into the vein is restricted to that required to guide the dilator (20.5 cm) into the venous system and further advancement prevented while inserting the dilator and sheath, the incidence of arrhythmias is reduced by more than 70%. In addition, complex ventricular arrhythmias do not occur under these controlled conditions. This length of guidewire allowed into the vein is consistent with the recommended approach by the introducer kit manufacturer. If a shorter length of guidewire is inserted, even fewer arrhythmias may occur; however, guidewire stability and sterility may become a problem. For the purpose of this study, a second person secured the guidewire in group 2 patients, but the guidewire can be controlled by one person with close attention to the external length of wire. An adequate skin incision (easing dilator introduction) and clamping the distal guidewire to a sterile towel with a hemostat can facilitate safe insertion.

In summary, without strict attention to guidewire control, arrhythmias commonly occur with the Seldinger technique of right internal jugular vein cannulation. The incidence and severity of the arrhythmias are reduced with proper attention to the length of guidewire allowed to enter the venous system. The incidence of arrhythmias was approximately the same in the uncontrolled group as that of PA catheterization in the critically ill. Although the arrhythmias occurring in our group of stable cardiac surgical patients were not clinically significant, the precipitation of a clinically significant or life-threatening arrhythmia by venous cannulation may occur, perhaps especially in critically ill patients.

## References

1. Elliott CG, Zimmerman GA, Clemmer TP. Complications of pulmonary artery catheterization in the care of critically ill patients. A prospective study. Chest 1979;76:647–52.
2. Sprung CL, Pozen RG, Rozanski JJ, Pinero JR, Eisler BR, Castellanos A. Advanced ventricular arrhythmias during bedside pulmonary artery catheterization. Am J Med 1982;72:203–8.
3. Sprung CL, Marcial EH, Garcia AA, Sequeira RF, Pozen RG. Prophylactic use of lidocaine to prevent advanced ventricular arrhythmias during pulmonary artery catheterization. Prospective double-blind study. Am J Med 1983;75:906–10.
4. Salmenpera M, Peltola K, Rosenberg P. Does prophylactic lidocaine control cardiac arrhythmias associated with pulmonary artery catheterization? Anesthesiology 1982;56:210–2.
5. Sprung CL, Jacobs LJ, Caralis PV, Karpf M. Ventricular arrhythmias during Swan–Ganz catheterization of the critically ill. Chest 1981;79:413–5.

# Peripheral Nerve Stimulation Through a Local Anesthetic Path:

## A Modified Koons Technique

Thomas G. Johans, MD, and George Carr, MS

Regional nerve blockade is considered to be less painful and more successful when a peripheral nerve stimulator (PNS) is used to localize the nerve (1,2). Because the needle is placed with more accuracy, the chance for nerve damage and local anesthetic toxicity is decreased.

Although this technique can be performed without insulated needles (3), there is recent evidence (4,5) that supports the use of an insulated needle. It is unfortunate however, that such needles are expensive and not readily available.

In 1969, Koons (2) overcame these drawbacks by using the "Rochester" intravenous (IV) "extra-cath" as an insulated needle. To conduct the stimulating electrical impulses to the needle tip, he attached the stimulating electrode of the PNS via a stainless steel stopcock to the stainless steel hub of the obturator needle. Unfortunately, obturator needles used in commercially available IV extra-cath today are manufactured with nonconductive plastic hubs. Hence this otherwise ingenious and inexpensive insulated needle is no longer used.

We thought that if an electrocardiographic impulse could be conducted along a saline-filled catheter during right atrial electrocardiography (6), then the impulse of the PNS possibly could be conducted through the local anesthetic that fills the plastic hub of the IV extra-cath. This innovation would then reestablish the IV extra-cath needle as an inexpensive, ubiquitously available, insulated block needle. The purpose of this report is to illustrate that the equipment apparatus described by Koons remains applicable even without stainless steel obturator needle hubs, to present a modification that makes the technique more aseptic and less cumbersome, and to provide supporting evidence that the increased resistance imposed by this modification does not preclude its use.

## Equipment Modification

In the apparatus described by Koons, a stainless steel stopcock is interposed between the syringe containing the local anesthetic and the IV extra-cath needle (2) (Fig. 1). To make this less cumbersome, we modified it with the immobile needle technique of Winnie (1) by interposing a length of disposable extension tubing between the stainless steel stopcock and the IV extra-cath needle (Fig. 1). The stimulating electrode of the PNS was then clipped by an alligator clamp to the stainless steel stopcock. (Because stainless steel stopcocks are expensive and nondisposable, we chose to use the Arrow–Johans™ Right Atrial Electrocardiography Adaptor, Arrow International, Inc., Reading, PA EG-04900.) The stainless steel stopcock provides the necessary wire-to-solution adapter. The entire system is then flushed with the local anesthetic, and bubbles are meticulously removed. Using this equipment, the technique is carried out in a manner similar to Koons (2) or Montgomery et al. (3).

## Materials and Methods

The equipment apparatus as described by Koons, as well as the proposed modification, was studied. A known 1000-Ω resistor was placed in series with the IV tubing filled with local anesthetic solution and the PNS. To measure the voltage drop ($V$) across this resistor, a Tektronix 464 storage oscilloscope was placed in parallel with the resistor. Output current delivered by the PNS to the tip of the needle could then be related as $V/1000$. Two concentrations of both ester and amide local anesthetics were studied. The Dupaco 54120 Peripheral Nerve Stimulator (Dupaco Inc., San Marcos, CA) was used as the test stimulator and was charged with a fresh 9-V battery. Measurements were made at each amplitude setting on the Dupaco PNS at 2 Hz frequency. Three IV extension tubings

---

Received from the Department of Anesthesiology, St. John's Mercy Medical Center, St. Louis, Missouri. Accepted for publication June 25, 1985.

Address correspondence to Dr. Johans, Department of Anesthesiology, St. John's Mercy Medical Center, 621 South New Ballas Road, St. Louis, MO 63141.

© 1985 by the International Anesthesia Research Society

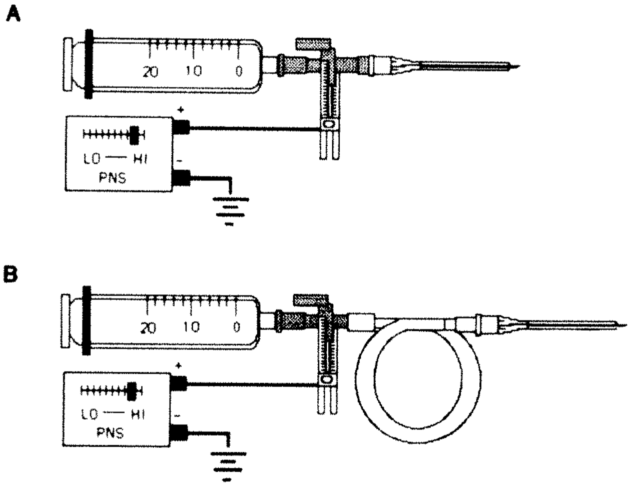


Figure 1. Equipment apparatus described by Koons. The stimulating current is conducted via a stainless steel stopcock to the stainless steel hub of the obturator needle (*A*). The Koons equipment apparatus is modified with the immobile needle technique of Winnie. The stimulating current is conducted via local anesthetic-filled intravenous extension tubing (*B*).

Table 1. Output Current (mA) at 5 PNS Amplitude Settings from Intravenous Tubings of Varying Dimensions

| Intravenous tubing dimensions | PNS amplitude settings | | | | |
|---|---|---|---|---|---|
| | 5 | 4 | 3 | 2 | 1 |
| 0.5-in 2.5-mm[a] | 20 | 15 | 10 | 5 | 0 |
| 22.0-in 2.5-mm | 4 | 3 | 2 | 1 | 0 |
| 33.0-in 2.5-mm | 2 | 1.5 | 1 | 0.5 | 0 |
| 6.0-in 1.5-mm | 3 | 2.5 | 1.5 | 0.5 | 0 |

[a] Dimensions of extra-cath obturator needle hub, inner diameter.

All measurements made across a 1000-Ω resistor with 2% lidocaine HCl as the local anesthetic.

were assessed: a 33-in 2.5-mm inner diameter (Medex, Hilliard, OH); a 20-in 2.5-mm inner diameter (Pharmaseal Inc., Toa Alta, Puerto Rico); and a 6-in 1.5-mm inner diameter (Linton Biomed Corporation, Mercer Island, WA).

## Results

There was no difference in output current resulting from varying the concentration, the class (ester vs amide) of the local anesthetic, or both. Table 1 lists the output current with the five PNS amplitude settings at varying IV extension tubing dimensions.

## Discussion

Local anesthetics are weak electrolytic solutions that conduct electric current depending on the degree of their ionic dissociation. Commercially prepared local anesthetic solutions are maximally dissociated because they are acidified well below their pKa to insure water solubility. A local anesthetic-filled tubing, therefore, will act like an insulated wire. The highest transfer of current would be expected from IV tubing of largest diameter and shortest length (7). It is no surprise, then, that the short length of the plastic needle hub (Table 1) conducted the most current. There need not be concern over stainless steel obturator hubs, as cited by Koons (2). The technique continues to provide the least expensive and universally available insulated block needle. Although IV tubing of greater diameter and shorter length can be purchased, one of the advantages of this technique is equipment availability. For this reason we tested only the IV extension tubing available from our hospital stock.

We have found, however, that having the alligator clip close to the needle is cumbersome and threatens contamination. We overcame this drawback by incorporating the immobile needle technique of Winnie (1). This technique allows the needle to be stabilized during aspiration and injection of the local anesthetic without dislodging the needle tip (1). In addition, it allows the anesthetist to remain sterile without threat of contamination by the nonsterile stimulating wire and alligator clip.

Despite a marked decrease in output current with varying dimensions of tubing, all delivered the minimum range of current (0.5–2.0 mA) required to perform this technique (5,8). The addition of this local anesthetic-filled IV extension tubing, therefore, does not increase the resistance enough to preclude its use. Compared to the high current output of the Koons apparatus, however, the increased resistance does decrease the sensitivity of the technique (that is, at the same PNS amplitude, the needle tip must be closer to the nerve for stimulation). This loss of sensitivity would make stimulation of peripheral nerves located deep in the tissue (i.e., the sciatic nerve) more difficult. Fortunately, this loss of sensitivity is balanced with an increase in specificity (that is, the needle tip is closer to the nerve for the same stimulation). This increase in specificity would make superficial nerve location (i.e., with brachial plexus) more accurate by overcoming false positive nerve twitches from high output current. Even though specificity can be increased with manipulation of the PNS amplitude, the current output at PNS settings other than maximum has been reported to be extremely variable (9). In the absence of commercially available constant current stimulators, the type of nerve block may, in the meantime, dictate the equipment apparatus.

Special mention should be made about air bubbles. As they will completely stop conduction, a meticulous effort should be made to remove them. They most commonly arise from aspirating immediately upon skin puncture. The large negative pressure created by aspiration forms bubbles in the hub of the needle. This problem can best be avoided by delaying aspiration until the needle is correctly placed and the need for stimulation over.

We have used this modification for patients undergoing peripheral nerve blockade during the past year and have found it to be as successful but less cumbersome than the equipment apparatus described by Koons. Special insulated needles designed to be less neuropathic (10) are being introduced commercially. Until they become more available and less expensive, we think this technique offers a practical alternative.

The authors are indebted to Drs. Kenneth Keown and G.W.N. Eggers for their critical review, to Mr. Jimmy Birkenbach for his electronic expertise, and to Ms. Emilie A. Sommer for her secretarial assistance.

## References

1. Winnie AP. Plexus anesthesia. Volume 1: perivascular techniques of brachial plexus block. Philadelphia: W.B. Saunders Company, 1983:215–8.
2. Koons RA. The use of the block-aid monitor and plastic intravenous cannulas for nerve blocks. Anesthesiology 1969;31:290–1.
3. Montgomery SJ, Raj PP, Nettles D, Jenkins MT. The use of the nerve stimulator with standard unsheathed needles in nerve blockade. Anesth Analg 1973;52:827–31.
4. Bashein G, Haschke RH, Ready B. Electrical nerve location: numerical and electrophoretic comparison of insulated vs uninsulated needles. Anesth Analg 1984;63:919–24.
5. Douglas JF, Pither C, Raj PP. Comparison of insulated and uninsulated needles for locating peripheral nerves with a peripheral nerve stimulator. Anesth Analg 1984;63:925–8.
6. Martin JT. Neuroanesthetic adjuncts for patients in the sitting position: III. Intravascular electrocardiography. Anesth Analg 1970;49:793–805.
7. Rosenbaum EJ. Physical chemistry. New York: Meredith Corporation, 1970:598–600.
8. Galindo A. Illustrated regional anesthesia. Miami: RM Scientific Publications, 1982.
9. Mylrea KC, Hameroff DR, Calkins JM, et al. Evaluation of peripheral nerve stimulators and relationship to possible errors in assessing neuromuscular blockade. Anesthesiology 1984;60:464–6.
10. Galindo A, Galindo A. Special needle for nerve blocks. Reg Anesth 1980;5:12–3.

1220 ANESTH ANALG
1985;64:1220–2

# Prolonged Neuromuscular Blockade with Vecuronium in a Patient Treated with Magnesium Sulfate

Raymond S. Sinatra, MD, PhD, Beverly K. Philip, MD, J. Stephen Naulty, MD, and Gerard W. Ostheimer, MD

Magnesium sulfate ($MgSO_4$) is widely utilized in the treatment of preeclamptic hyperreflexia. Such therapy has important anesthetic implications because increases in plasma magnesium potentiate the activity of both depolarizing and nondepolarizing neuromuscular blocking agents (1). In a recent animal study, Tran et al. (2) reported significant interaction between $MgSO_4$ and vecuronium, a nondepolarizing muscle relaxant of intermediate duration. Although vecuronium dose requirements in patients treated with $MgSO_4$ have yet to be determined, we present a case in which marked prolongation of neuromuscular blockade occurred after use of vecuronium in a patient being treated with $MgSO_4$.

## Case Report

A 40-yr-old, 58-kg gravida 3, para 2 at 34 weeks gestation and in active labor was transferred to the Brigham and Women's Hospital with signs of severe preeclampsia. Her blood pressure on admission was 160/110 mm Hg, urine protein was 4+, and reflexes were 3+ with 8–9 beats of clonus. The patient, lethargic yet cooperative, had no history of significant medical illnesses, allergies, medications, or anesthetic complications.

Although she had received 4 g $MgSO_4$ intravenously before transfer from the referring hospital, continued hyperreflexia necessitated an additional 4 g intravenous bolus followed by a 2 g/hr continuous intravenous infusion. Approximately 30 min after the second bolus, sudden and severe late decelerations of the fetal heart rate mandated immediate cesarean delivery before maternal hematocrit, coagulation profile, and serum magnesium level (6.1 mEq/L on admission) became available. The patient was given 30 ml of clear liquid antacid and quickly moved to the operating room where 100% oxygen was administered prior to a rapid sequence intravenous induction with thiopental (4 mg/kg), succinylcholine (1.5 mg/kg), and cricoid pressure. After tracheal intubation, anesthesia was maintained with 50% $N_2O$/50% $O_2$ and enflurane, 1.0%, until delivery of a viable 1500 gm infant (approximately 6 min after skin incision). Apgar scores were 5 and 8 at 1 and 5 min, respectively. After delivery, enflurane was discontinued and substituted with a 70% $N_2O$–narcotic (fentanyl 50 $\mu$g) technique. Central and large-bore peripheral catheters were placed to monitor and treat hypovolemia secondary to severe preeclampsia and an acute 600 ml intraoperative blood loss.

Muscle relaxation, assessed by train-of-four stimulation of the ulnar nerve, did not require reinforcement until 10 min after succinylcholine administration when return of twitch response and patient movement were noted. Vecuronium (Norcuron, Organon Pharmaceuticals) 3 mg (50 $\mu$g/kg) was then administered for maintenance of relaxation.

After administration of lactated Ringer's solution (3.5 L), the remainder of the 70-min procedure was uneventful except that no twitch response could be elicited. For this reason we discontinued the $MgSO_4$ infusion 50 min into the procedure and obtained venous blood samples for measurement of serum magnesium levels (intraoperative level 6.2 mEq/L). Surgery was completed approximately 60 min after vecuronium administration, and reversal of pronounced neuromuscular blockade (absent twitch, minimal ulnar or facial nerve response after 50 Hz stimulation) was attempted with intravenous neostigmine (4 mg) and atropine (1.6 mg).

Emergence from anesthesia was rapid, but the patient appeared weak and had only two to three twitches in response to train-of-four stimulation. She was re-

---

Received from the Department of Anesthesia, Brigham and Women's Hospital and the Harvard Medical School, Boston, Massachusetts. Accepted for publication June 27, 1985.

Address correspondence to Dr. Sinatra, Department of Anesthesiology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510.

© 1985 by the International Anesthesia Research Society

assured, sedated with diazepam, and treated with additional neostigmine (1 mg). After 45 min of assisted ventilation she was, however, still unable to sustain head lift and could only manage a 200 ml maximum expiratory volume and a 10 cm (water) negative inspiratory pressure. The patient was transferred to the recovery area for an additional 1.5 hr of ventilatory assistance and then tolerated breathing via a T-piece. She was extubated 3.5 hr after receiving the single dose of vecuronium and subsequently had an uneventful postoperative course.

## Discussion

Vecuronium is a useful nondepolarizing muscle relaxant in healthy parturients undergoing cesarean delivery; it is associated with minimal placental transfer and a more rapid elimination half-life than that observed in nonpregnant patients (3). Vecuronium also offered theoretical advantages for the management of our patient, including intermediate duration of effect, negligible histamine release, and cardiovascular stability (4).

Potentiation of neuromuscular blockade should be expected and dosage adjusted whenever magnesium–relaxant combinations are employed. In the present case, some potentiation of vecuronium activity was anticipated; however, as the time required for completion of surgery was believed to be more than twice the duration of the dose administered (4), a moderately prolonged relaxation interval could have been accommodated. The resulting magnitude of prolongation as evidenced by an 8-fold increased duration of action was unexpected. Such prolongation was surprising because the interval of succinylcholine-induced relaxation was not appreciably greater than that observed in parturients not given $MgSO_4$.

Factors that might have increased vecuronium's duration of action include too large a dose being administered for this patient's decreased weight and volume of distribution after delivery of the baby and placenta, and potentiation by residual succinylcholine and an inhalational anesthetic. However, return of twitch response was normal prior to vecuronium administration and enflurane was discontinued after delivery. The most reasonable explanation for the prolongation of vecuronium activity in this case was the therapeutically induced elevation of plasma magnesium.

Magnesium sulfate is a drug of choice in preeclamptic individuals because its depressant effect upon the central nervous system and neuromuscular junction (NMJ) effectively reduces hyperreflexia and may prevent grand mal seizures. Therapeutic plasma levels, which lie between 4 and 6 mEq/L, may, however, suppress peripheral neuromuscular function by decreasing acetylcholine release (5). Reduction of endplate sensitivity and decreased muscle fiber excitability have also been reported (6). Progressive maternal weakness occurs as plasma magnesium levels approach 12–15 mEq/L (7). In the present case, perioperative magnesium levels were at the upper end of the therapeutic range. Therefore, magnesium toxicity by itself was probably not responsible for the prolonged paralysis. This observation suggests that vecuronium requirements are significantly lower in patients with therapeutic plasma magnesium levels. The validity of this impression is strengthened by findings in rabbits where the vecuronium $ED_{50}$ decreased in linear fashion as plasma magnesium levels increased from 2 to 6 mEq/L (2).

Generalized depression of the NMJ could easily influence the duration of vecuronium activity by reducing the number of functional cholinergic receptors or the amount of acetylcholine available to overcome competitive blockade. A similar conclusion was first reported by Morris and Giesecke (8), who found that $MgSO_4$ had 1/1000 the potency of *d*-tubocurarine and additive effects when administered with either depolarizing or nondepolarizing agents. In contrast to these findings, prolongation of succinylcholine blockade was not significant and did not influence the management of our patient. Moreover, the interaction between vecuronium and $MgSO_4$ appears to be more pronounced than that occurring with *d*-tubocurarine and $MgSO_4$ where one-half the usual dose is recommended for adequate maintenance of relaxation (9). Because vecuronium is approximately nine times as potent as *d*-tubocurarine, interactions with magnesium may become magnified and result in prolonged and profound inactivation of the NMJ in a manner not predicted by pharmacokinetic profiles.

In conclusion, therapeutic levels of magnesium greatly increased the duration of vecuronium activity in a preeclamptic patient. It is recommended that vecuronium be carefully titrated to twitch response in parturients receiving magnesium salts.

## References

1. Ghoneim MM, Long JP. The interaction between magnesium and other neuromuscular blocking agents. Anesthesiology 1970;32:23–7.
2. Tran B, Nguyen B, Chung H, Murad S, Lee C. Interaction between magnesium and vecuronium in rabbits. Anesthesiology 1984;A403.
3. Dailey PA, Fisher DM, Shnider SM, Baysinger CL, Shinohana Y, Miller RD, Abboud TK, Kim KC. Pharmacokinetics, placental transfer and neonatal effects of vecuronium and pancuronium

# Letters to the Editor

## Midazolam Maleate and Hydrochloride

To the Editor:

The findings reported by Blackmon et al. (1) are not unexpected. In crossover studies in 11 subjects, we found no significant difference in mean plasma levels after injection of 0.1 mg/kg of the two salts (2) (see Fig. 1).

J. W. Dundee, MD, PhD, FRCP, FFARCS
P. Kawar, MD, PhD
*Department of Anaesthetics*
*The Queen's University of Belfast*
*Whitla Medical Building*
*97 Lisburn Road*
*Belfast BT9 7BL*
*Northern Ireland*

### References

1. Blackmon BB, Mahaffey JE, Baker JD. Clinical comparison of midazolam hydrochloride and midazolam maleate for anaesthesia induction. Anesth Analg 1984;63:1116–20.
2. Kawar P, Dundee JW, Gamble JAS, Collier PS, Howard PJ. Benzodiazepine pharmacokinetics: some observations with midazolam and diazepam. Summaries of VI European Congress of Anaesthesiology, Paper No. 449. London: Academic Press, 1982:5.

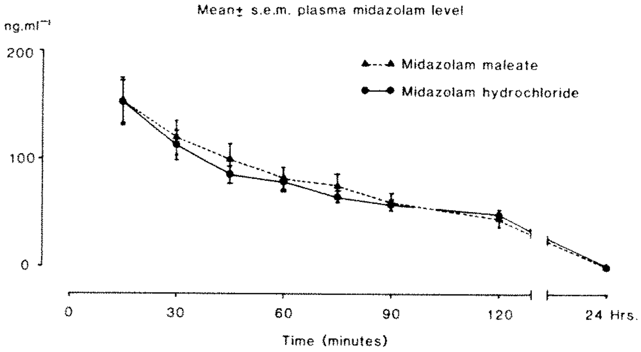


Figure 1. Mean plasma midazolam levels.

## The Effect of Chloroprocaine on Neonatal Neurobehavior

To the Editor:

The Brazelton Neonatal Behavioral Assessment Scale (BNBAS) (1) is sensitive to very subtle effects of low levels of drugs given to the mother during labor and delivery (2–4). It may be more sensitive than the Scanlon Early Neonatal Neurobehavioral Scale (ENNS) (5) or the Neurologic and Adaptive Capacity Scoring System (NACS) (6), both of which emphasize changes in muscle tone or diminished response to decrement. The reason for the greater sensitivity of the BNBAS may be that it evaluates many aspects of the newborn's behavioral repertoire, including reflexes, physiologic response to certain stresses, irritability/consolability, and a number of social–interactive behaviors thought to be important to the care giver.

The regulation of state cluster (8) of the BNBAS appears to be particularly sensitive to drugs. In the past, we have reported that low doses of meperidine given to the mother have measurable effects on this cluster (2). Nonmedicated control neonates showed significant improvement in scores with age while neonates born of mothers given meperidine showed none. In an earlier study, we also reported that there was no such improvement with age on this cluster in infants whose mothers received lidocaine or chloroprocaine for epidural anesthesia (3).

While it is known that lidocaine may have subtle effects on the BNBAS, chloroprocaine has often been considered a "control" for neurobehavioral studies of local anesthetics (4). However, there have been no direct comparisons of chloroprocaine with a concurrent nonmedicated control group. For this reason, we would like to report a comparison of BNBAS scores of vaginally delivered infants whose mothers received chloroprocaine for epidural anesthesia ($n$ = 13) and a concurrent control group of infants who were delivered without maternal medication ($n$ = 16). Examinations were done on the first and third days of life. The methods and clinical characteristics of the patients have been reported previously (2,3).

Significant differences in the clinical characteristics of the two groups were found only in the length of labor and parity

© 1985 by the International Anesthesia Research Society

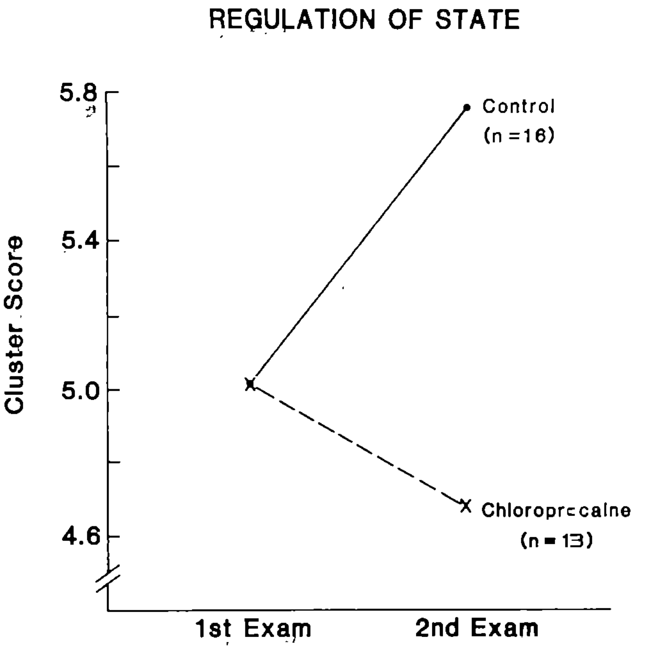


Figure 1. The effect of chloroprocaine on the infant's recovery on the regulation of state cluster.

($P < 0.05$); individuals in the control group were more parous and had shorter labors. Because of these differences, length of labor and parity were each used as covariates in separate repeated measures analyses of variance (ANOVAS) that looked at the effect of drug and test day on the BNBAS clusters.

The results showed that there was one significant effect of chloroprocaine and this was on the regulation of state cluster (Fig. 1). There was a significant improvement in test scores in the control group but not in the epidural group ($P = 0.015$). The effects of chloroprocaine were obvious on the third day when the differences between the means were greater than one scale point. Standard deviations were 1.03 and 1.01 for the control group on the first and second examinations, and 1.09 and 1.10 for the chloroprocaine group on the first and second examinations. The difference was statistically significant when controlling for length of labor and parity between the groups.

The regulation of state cluster includes items that measure the infant's cuddliness, consolability, self-quieting, and hand-to-mouth activity (8). These items are thought to be important because they may influence maternal–infant interaction (8). Thus this study suggests that chloroprocaine may have subtle neurobehavioral effects on the infant. Therefore, chloroprocaine may not be completely innocuous and should not be used as a "control" for studies on the effects of drugs on neonates using BNBAS.

Betty R. Kuhnert, PhD
Patricia L. Linn, PhD
*Perinatal Clinical Research Center and Dept. of Ob/Gyn*
*Case Western Reserve University*
*Cleveland Metropolitan General Hospital*
*3395 Scranton Road*
*Cleveland, OH 44109*

## References

1. Brazelton TB. Neonatal behavioral assessment scale. Philadelphia: Lippincott, 1973:1–66.
2. Kuhnert BR, Linn PL, Kennard MJ, et al. Effects of low doses of meperidine on neonatal behavior. Anesth Analg 1985;64:335–42.
3. Kuhnert BR, Harrison MJ, Linn PL, et al. Effects of maternal epidural anesthesia on neonatal behavior. Anesth Analg 1984;63:301–8.
4. Kuhnert BR, Linn PL, Kuhnert PM. Obstetric medication and neonatal behavior—Current controversies. Clin Perinatol 1985;12:423–40.
5. Scanlon JW, Brown WU, Weiss JB, et al. Neurobehavioral responses of newborn infants after maternal epidural anesthesia. Anesthesiology 1974;40:121–8.
6. Amiel-Tison C, Barrier G, Shnider SM, et al. A new neurologic and adaptive capacity scoring system for evaluating obstetric medications in full-term newborns. Anesthesiology 1982;56:340–50.
7. Als H. Assessing an assessment: conceptual considerations, methodological issues, and a perspective on the future of the neonatal behavioral assessment scale. In Sameroff AJ (ed), Organization and stability of newborn behavior: a commentary on the Brazelton neonatal behavior assessment Scale. Mongr Soc Res Child Dev 1978;43:14–28.
8. Lester BM, Als H, Brazelton TB. Regional obstetric anesthesia and newborn behavior: a reanalysis toward synergistic effects. Child Dev 1982;53:687–92.

---

# Humidifiers Are Unjustified in Adult Anesthesia[1]

To the Editor:

When confronted with a clinical situation where intraoperative hypothermia may occur, the anesthesiologist using a circle system has two options: use a heated humidifier or close the circuit. The closed circuit provides essentially ideal inspired humidity (1). This is accomplished by conserving expired humidity and by converting expired carbon dioxide to water. The closed circuit plus the considerable heat- and moisture-exchanging properties of the endotracheal tube combine to provide humidification comparable to a conscious subject breathing through his nose (2). Any possible adverse physiologic effects of dry anesthetic gases are prevented by the closed circuit. However, many anesthesiologists feel that heated humidifiers actively warm a patient who has been allowed to get cold. The article by Railley et al. (3) dispels this myth. As shown in their enlightening thermodynamic discussion, two-thirds of the potential thermal benefit of a humidifier comes from conservation of humidified gases. In related work, Sims and Welch (4) carefully measured temperature gradients along the endotracheal tube and showed that previous claims for heated humidification were overstated. These careful analyses indicate that there is no reason to believe that a heated humidifier can provide a significant advantage over the closed circuit.

---

[1] The opinions or assertions contained herein are the private views of the author and are not to be construed as reflecting the views of the Department of the Army or the Department of Defense.

High flow systems replaced the closed circuit in an era when humidification and intraoperative hypothermia were not viewed as significant problems. In that era, closed circuit anesthesia had technical limitations that have been completely solved in the intervening years. Until the late 1940s, indicators were not commonly used in carbon dioxide absorbent, so considerable clinical judgment was required for changing absorbent when the circuit was closed. Double canisters with indicators now allow safe optimal use of absorbent. An oxygen analyzer is an important safety feature in closed circuit anesthesia and is mandatory whenever nitrous oxide is used. Oxygen analyzers were marketed in the 1970s and are now viewed as essential in all anesthetizing locations (5). Finally, the quantitative pharmacokinetic understanding required for closed circuit administration of potent volatile agents was developed in the early seventies (6). The quantitative administration of potent volatile agents in the closed circuit requires only an inexpensive pocket calculator (also a development of the 1970s).

Before a new medication can be marketed, manufacturers must demonstrate that the medication has advantages in safety or efficacy over medications already available. The same standard should also apply to anesthesia equipment. Humidifiers should not be marketed for adult use until randomized studies demonstrate a significant advantage over the closed circuit, a highly unlikely outcome. A beneficial effect must be demonstrated on some measure of total body heat content, not simply warming an esophageal temperature probe (7). Pediatric closed circuit anesthesia requires a specially designed pediatric absorber (8,9). Because this equipment is not readily available, humidifiers are probably justified in pediatric anesthesia at this time.

Humidifiers are expensive. A typical one lists for $750 with disposable, single use heating elements that cost $12. The addition of an expensive piece of equipment to an already crowded workplace is illogical when the same benefit accrues at no cost to the patient by simply lowering the flows. Anesthesiologists are highly paid consultants. In this era of cost containment, the patient should expect his anesthesiologist to acquire the necessary knowledge to safely practice closed or low flow techniques rather than be charged for an expensive humidifier.

R. K. Baumgarten, MD
*Department of Surgery,*
*Anesthesia and Operative Service*
*Brooke Army Medical Center*
*Fort Sam Houston, TX 78234-6200*

## References

1. Aldretti JA, Cubillos P, Sherrill D. Humidity and temperature changes during low flow and closed system anaesthesia. Acta Anaesthesiol Scand 1981;25:312–4.
2. Dery R, Pelletier J, Jacques A, et al. Humidity in anaesthesiology. II. Heat and moisture patterns in the respiratory tract during anaesthesia with the semi-closed system. Can Anaesth Soc J 1967;14:287–98.
3. Railley FE, Ramsey JG, Wyands JE, et al. Effect of humidified gases on the temperature drop after cardiopulmonary bypass. Anesth Analg 1984;63:1106–10.
4. Sims NM, Welch JP. Temperature gradients within anesthesia breathing circuits when heated humidification is used. Anesthesiology 1984;61:A150.
5. Dorsch SE, Dorsch JA. Use of oxygen analyzers should be mandatory. Anesthesiology 1983;59:161–2.
6. Lowe SL, Ernst EA. Uptake and distribution: square root of time model. In: The quantitative practice of anesthesia: use of the closed circuit. Baltimore: Williams and Wilkins, 1981:67–98.
7. Hendricks HHL, Trahey GE, Argentieri MP. Paradoxical inhibition of decreases in body temperature by use of heated and humidified gases. Anesth Analg 1982;61:393–4.
8. Chalon J, Simon R, Ramanathan S, et al. A high-humidity circle system for infants and children. Anesthesiology 1978;49:205–7.
9. Couta da Silva JM, Tubino PJ, Viera ZEG, Saraiva RA. Closed circuit anesthesia in infants and children. Anesth Analg 1984;63:765–9.

---

# Seizures from Isoflurane?

To the Editor:

Dr. J. A. Hymes doesn't think much of anecdotal reports. In his paper, "Seizure Activity during Isoflurane Anesthesia" (1), he writes, "Even though seizures have been implicated as a consequence of high doses of fentanyl, only anecdotal reports and no EEG evidence of seizures have been published." He then provides us with an anecdotal report of seizures without EEG evidence, this time attributed to isoflurane.

For general anesthesia, Dr. Hymes's patients received fentanyl, *d*-tubocurarine, thiopental, succinylcholine, nitrous oxide, and isoflurane. Seizures (increased muscle tone, myoclonus, muscle spasticity) occurred during operation and persisted (myoclonus) for at least 1 hr after operation. Slowly eliminated fentanyl has a seizure–anecdote–score of five patients (2–5); rapidly eliminated isoflurane has a seizure–anecdote–score of zero. Which is the most likely cause of seizure? But then you can't believe anecdotal reports of seizures without an EEG anyway.

Arthur S. Keats, MD
*Division of Cardiovascular Anesthesia*
*Texas Heart Institute*
*Houston, TX 77025*

## References

1. Hymes JA. Seizure activity during isoflurane anesthesia. Anesth Analg 1985;64:367–8.
2. Rao TLK, Mummaneni N, El-Etr AA. Convulsions: an unusual response to intravenous fentanyl administration. Anesth Analg 1982;61:1020–1.
3. Safwat AM, Daniel D. Grand mal seizure after fentanyl administration. Anesthesiology 1983;59:78.
4. Hoien AO. Another case of grand mal seizure after fentanyl administration. Anesthesiology 1984;60:387.
5. Baraka A, Haroun S. Grand mal seizures following fentanyl–lidocaine. Anesthesiology 1985;62:206.

In Response:

Anecdotal reports are almost invariably the initial form for the presentation of new and previously unexpected events. Clinical and experimental studies characteristically follow them should enough questions be raised by these reports. The author must agree with Dr. Keats that more cases of seizures have been reported associated with fentanyl than with isoflurane. The only inference that can be drawn from this, however, is that if there is really an incidence of seizures with either drug, it is extremely rare. The approach of using a seizure–anecdote–score as an attempt to quantify these anecdotal reports is an innovative one but cannot possibly serve to confirm the occurrence of seizures with one drug while denying the other. Rather, it can only show the perhaps very unusual nature of the incidence with each. Interestingly enough, since the beginning of anecdotal reports of seizure activity associated with fentanyl, clinical investigative studies have been carried out. To date, EEG substantiation of seizure activity associated with fentanyl anesthesia (at least in high dose fentanyl anesthesia) remains absent (1).

In examining other anecdotal reports of seizure activity also associated with fentanyl, a substantial difference exists between circumstances in this reported case, and those previously reported (2–5). Dr. Keats indicates that isoflurane is eliminated rapidly, whereas fentanyl takes more time. This is the case. However, the primary determinant of the duration of action of fentanyl in low doses (as in this case) is that of redistribution from the vessel-rich brain. In this instance there was a time interval of greater than one-half hour from the administration of the 100-$\mu$g bolus of fentanyl until the slowly progressive onset of seizure activity. In a patient without otherwise complicating medical conditions, the fentanyl level in the brain should be exceedingly low.

It should also be noted that of all the drugs listed as given in the case that may potentially complicate the situation, i.e., fentanyl, *d*-tubocurarine, thiopental, succinylcholine, nitrous oxide, and isoflurane, only fentanyl (and now isoflurane) have been implicated as potentially causing seizure-like activity.

The utilization of intraoperative encephalographic monitoring is, and may always be, the exception rather than the rule in all but a select number of cases. This fact, coupled with the clear rarity of seizure activity with either of the above-mentioned drugs, makes the likelihood of observing it on an EEG very low. In fact, when specifically looked for under the appropriate circumstances, they did not occur (1).

Finally, it should be noted that if one cannot believe anecdotal reports of seizures without the assistance of a relatively recent invention such as an electroencephalogram, epilepsy would be a very young disease indeed.

Jayson A. Hymes, MD, MPH
*Emory University School of Medicine*
*Atlanta, GA*

References

1. Murkin JM, Moldenhauer CC, Hug CC Jr, Epstein CM. Absence of seizure during induction of anesthesia with high dose fentanyl. Anesth Analg 1984;63:489–94.
2. Baraka A, Haroun S. Grand mal seizures following fentanyl–lidocaine. Anesthesiology 1985;62:206.
3. Safwat AM, Daniel D. Grand mal seizure after fentanyl administration. Anesthesiology 1983;59:78.
4. Hoien AO. Another case of grand mal seizure after fentanyl administration. Anesthesiology 1984;60:387.
5. Hymes JA. Seizure activity during isoflurane anesthesia. Anesth Analg 1985;64:367–8.

---

## Seizures with Etomidate Anesthesia

To the Editor:

We read with interest the case reported by Laughlin and Newberg (1), describing a patient with prolonged myoclonus after an etomidate infusion combined with $N_2O$ and pancuronium for operative anesthesia. The patient developed facial twitching shortly after surgery that spread to become generalized myoclonus. The patient was unresponsive during this time and had no memory for the event. The myoclonus lasted approximately 2.5 hr.

In our institution we have used etomidate to activate the seizure focus in patients undergoing temporal lobectomy for the treatment of medically refractory complex partial seizures. The patients are continuously monitored with cortically placed electrodes, and in more than 25 patients, etomidate consistently has activated the patients' epileptiform activity. This protocol was begun when anesthesia was induced with etomidate in a young patient allergic to barbiturates, scheduled for a cortical resection of epileptogenic tissue. After induction, but prior to muscle relaxation, the patient had a grand mal convulsion (2). After the craniotomy, electrodes were placed on the cortical surface, etomidate was administered, and again the seizure focus was activated inducing an electrographic seizure.

We have also given etomidate to more than 30 patients whose EEGs were being monitored while they were undergoing open heart surgery for valve replacements. None had a history of epilepsy. Approximately 20% of these patients, after etomidate induction, had generalized epileptiform activity recorded in their EEGs.

It is unfortunate that the patient reported by Laughlin and Newberg did not have an EEG performed during the prolonged period of myoclonus and altered consciousness. It is possible that at least part of this patient's behavior represented seizure activity induced by etomidate. Patients receiving etomidate who demonstrate abnormal somatic responses that possibly are epileptic in origin should have EEGs performed to rule out seizure activity.

Walter Krieger, MD
Jack Copperman, MD
*Department of Anesthesiology*

Kenneth D. Laxer, MD
*Department of Clinical Neurophysiology*
*Good Samaritan Hospital and Medical Center*
*Portland, OR 97210*

References

1. Laughlin TP, Newberg LA. Prolonged myoclonus after etomidate anesthesia. Anesth Analg 1985;64:80–2.
2. Gancher S, Laxer KD, Krieger W. Activation of epileptogenic activity by etomidate. Anesthesiology 1984;61:616–8.

---

# Possible Potentiation by Hydroxyzine of Metoclopramide's Undesirable Side Effects

To the Editor:

Adverse responses to hydroxyzine and metoclopramide have been reported when the drugs are administered separately (1–6). We now report an unexpected drug reactions after the administration of metoclopramide and hydroxyzine.

After a motor vehicle accident, a 20-yr-old previously healthy man was admitted for assessment and debridement of a left leg wound. Except for the left leg, physical and neurologic examinations were normal. Routine preoperative laboratory tests were normal. There was no clinical or biological evidence of drug or alcohol abuse. He had taken nothing by mouth since 11:30 AM (4 hr before the accident). The surgical procedure was scheduled for 9:00 PM. An hour before surgery, at 8:00 PM, to ensure gastric emptying, the patient was given 10 mg metoclopramide (0.15 mg·kg$^{-1}$). The drug was diluted and administered by injection into an intravenous infusion. Half an hour before surgery, at 8:30 PM, as surgical premedicant, the patient was given 100 mg hydroxyzine by deep intramuscular injection. At 9:00 PM, on his arrival in the operating room, instead of being sedated, he was anxious. During preparation for induction, rigidity and generalized tremor developed and the patient complained of diffuse pains. Within 5–7 min he became restless and confused: blood pressure increased from 120/70 to 190/110 mm Hg without tachycardia. Respirations became irregular and opisthotonos appeared. These symptoms responded rapidly to the intravenous administration of thiopental (10 mg·kg$^{-1}$), followed by halothane inhalation after airway control. The surgical procedure was performed without any further adverse events. Recovery was not notably delayed. No recurrence of the symptoms occurred. After complete recovery, complete physical and neurological examinations were normal, except for a temperature of 38.6°C. The fever subsided within 24 hr. The patient did not remember anything about the incident. He was discharged four days later.

After the administration of metoclopramide and hydroxyzine, this healthy young man without history of neurologic conditions developed acute anxiety and dystonia with elevation of blood pressure. These symptoms have already been reported after administration of metoclopramide alone (4–7). The average time to onset of metoclopramide-induced side effects is normally 24–48 hr (6) after initiation of the therapy. Occasionally side effects occur within 10–90 min (6), especially in children, in the presence of infections or when metoclopramide is associated with drugs such as phenothiazines, butyrophenones, thioxanthenes, and macrolides. Children and young adults are particularly prone to dystonic extrapyramidal-like reactions (6,7). Such reactions have most often been observed after large daily doses exceeding 0.5 mg·kg$^{-1}$. These reactions are sometimes accompanied by fever (4). Anticholinergic and antihistaminic drugs have been suggested for treatment of these reactions (4).

In our case, the patient received the usual therapeutic dose of metoclopramide (0.15 mg·kg$^{-1}$). However, instead of preventing an adverse reaction, hydroxyzine, an anticholinergic and antihistaminic drug, given intramuscularly 30 min after metoclopramide may well have precipitated it. Peak onset of hydroxyzine's therapeutic and adverse effects occurs 30–60 min after intramuscular injection (8–11). Our patient started to develop anxiety and dystonia 30 min after the intramuscular injection of hydroxyzine. This drug is known to be able to induce such neurological disorders as drowsiness, hypersedation, tremor, seizures (2,12), and, with chronic use, dyskinesia (13). In our observation, despite a seemingly appropriate dose of metoclopramide, the patient developed side effects usually reported after high doses. These side effects were observed 30 min after intramuscular hydroxyzine administration, at the time of peak onset of action of hydroxyzine. We suggest that hydroxyzine may have potentiated the onset of metoclopramide side effects.

On the base of a single case, it is not possible to be certain, but we draw attention to a possible interaction between metoclopramide and hydroxyzine.

Jean L. Fouilladieu, MD
Mireille Hosanski, MD
Kathleen McGee, MD
Milan Korvin, MD
Pierre Bonnette, MD
Yves Joulin
Christian Conseiller, MD
*Departments of Anesthesiology, General Surgery, and Clinical Pharmacology*
*Hopital Cochin*
*U.E.R. Cochin Port-Royal*
*27, rue du Faubourg Saint Jacques*
*75014 Paris, France*

References

1. Litchfield HR. Clinical pediatric experience with ataractic agent in less severe emotional states. NY State J Med 1960;60:518–23.
2. Prenner BM. Neonatal withdrawal syndrome associated with hydroxyzine hydrochloride. Am J Dis Child 1977;131:529–30.
3. McKenzie R, Wadhwa RK, Uy NTL, et al. Antiemetic effectiveness of intramuscular hydroxyzine compared with intramuscular droperidol. Anesth Analg 1981;305:783–8.

4. Harrington RA, Hamilton CW, Brogden RN, Linkewich JA, Romankiewicz JA, Hee RC. Metoclopramide. An updated review of its pharmacological properties and clinical use. Drugs 1983;25:451–94.
5. Albibi R, McCallum RW. Metoclopramide: pharmacological and clinical application. Ann Intern Med 1983;98:86–95.
6. Galland MC, Rodor F, Gratecos LA, Bourdillon N, Gailhaguet AM, Jouglard J. The metoclopramide undesirable side effects. Thérapie 1983;38:465–73.
7. Kris MG, Tyson LB, Gralla RJ, Clark RA, Allen JC, Reilly LK. Extrapyramidal reactions with high-dose metoclopramide. N Engl J Med 1983;309:433–4.
8. Fragen RJ, Funk DF, Avram MJ, Costello C, Debruine K. Midazolam versus hydroxyzine as intramuscular premedicant. Anesthesiology 1981;55:A278.
9. Vinik HR, Reves JG, Wright D. Premedication with intramuscular midazolam: a prospective randomized double-blind controlled study. Anesth Analg 1982;61:933–7.
10. Wallace G, Mindlin LJ. A controlled double-blind comparison of intramuscular lorazepam and hydroxyzine as surgical premedicants. Anesth Analg 1984;63:571–6.
11. Abouleish EI, Pan P. Placental transfer of hydroxyzine hydrochloride and its effects on human neonate. Anesth Analg 1984;63:176.
12. Magera BE, Betlach CJ, Sweatt AP, Derrick CW. Hydroxyzine intoxication in a 13 month old child. Pediatrics 1981;67:280–3.
13. Thach BT, Chase TN, Bosma JF. Oral facial dyskinesia associated with prolonged use of antihistaminic decongestants. N Engl J Med 1975;293:486–7.

# Book Reviews

## A Calculus of Suffering. Pain, Professionalism, and Anesthesia in Nineteenth Century America.

Martin S. Pernick. New York: Columbia University Press, 1985, illustrated, 421 pp, $35.00.

A fascination with the "discovery" of anesthesia still grips the minds of writers as shown in this latest example. M. S. Pernick approaches the phenomenon anew under the imposing rubric of "A Calculus of Suffering." The term is employed throughout the text, not in the medical or mathematical sense, but rather in the realm of symbolic logic—to pose a proposition. Here anesthesia is viewed in relation to concepts of professionalism and benevolence in 19th-century America, embracing such aspects as conservative and heroic medicine, and a cost benefit approach to medical ethics. Admittedly, the analysis and, especially the statistics, may be flawed by a chauvinistic use of sources that include only those non-American authors whose work touches upon American theory and by a narrow focus on how one generation of mostly eastern, urban professionals used anesthesia, and why. Pertinent in this context is the observation once made by medical historian C. E. Rosenberg, "Most medical practice was in the hands of uninformed, rural, semi-educated practitioners who leave few tracks in the archival sands."

Part I of this text reviews the fabric of 19th-century American medicine, heretofore amply described by others. Pernick notes, "Morton's demonstration of anesthesia in 1846 introduced a radically new remedy to a profession undergoing massive change." The writer does not hesitate to shun hyperbole, and was it indeed a remedy? Part II entitled "Why Not Everybody" embraces chapters concerning the basis for selective anesthetization, the drawbacks and the rivalry by other therapies and cults—hydropathy, vegetarianism, and homeopathy, for example. (Actually, a panorama of those times is nicely depicted in the American Society of Anesthesiologists' Exhibit on Pain, now at the Smithsonian Institution in Washington.) With considerable repetition, we are informed of the advantages of painlessness ("pain and fear can kill"), deliberate surgery, and medical paternalism whereby patients are relieved of the painful knowledge of what is being done to them. Several chapters speak of Utilitarian Professionalism, the Calculus of Safety, wherein choices must be made between suffering and death, of Competition and Consensus, and lastly the Ethics of Professional Decision Making.

The final chapters range from the universal to the particular, to deal with rules and regulations for anesthetization, which engendered the writing of textbooks, "Why Don't They Feel It The Way We Do" comes to the conclusion that general anesthesia was considered especially appropriate for children, women, the educated upper class, white persons, for major limb amputation, reduction of dislocations, and prolonged surgical dissections. Unfortunately, the supporting statistics are not amenable to verity analysis for the population base from which data are drawn is unknown.

This reviewer has several demurs. Can one assert that industrialization of society in those times increased anesthetic and surgical mortality, or was it the still unsolved specter of infection? Did the demand for operations increase with the advent of anesthesia, or were the operations merely still of the same superficial kind? Did anesthesia make it easier for women to specialize in surgery as contended here?

Overall, the "Calculus" represents a well-meaning and honest analysis—an historian's history that is hardly conducive to casual reading. This opinion is reinforced by the ten pages of statistics, nearly 100 pages of notes in reference to the text, some 50 pages of primary and secondary source material, and lastly an index. Had there been an anesthesiologist among those listed under acknowledgments, several apparent gaffes might have been avoided, such as the claims that Morton was the first to give anesthesia (perhaps Pernick implies the first public demonstration); that Edward Gilbert Abbott's lesion was a massive tumor of the face (a modest-sized congenital vascular anomaly of the neck); that the lesion was excised by surgeon J. C. Warren (mere ligation of the pedicle); that nitrous oxide began to be employed only after 1847 (widely used in dentistry after Well's extraction in 1844); that both Wells and Morton were merely opportunists (both men had a genuine urge to relieve the pain of dentistry); and that the anesthesia death rate in 1970 was one in 2000 operations (citing the Beecher–Todd study done around 1950).

Leroy D. Vandam, MD
*Brigham and Women's Hospital*
*Boston, MA*

© 1985 by the International Anesthesia Research Society

## Nitrous Oxide/$N_2O$.

Edmond I. Eger II, ed. New York, Elsevier Science Publishing Co., Inc., 1985, 369 pp, $37.50.

In the 140 years since its first medical use, nitrous oxide has been administered over a billion times to surgical, dental, and obstetrical patients. However, it is only within the last 30 years that many of the biophysical and biochemical correlates of nitrous oxide administration have been thoroughly studied. Because of his major role in these investigations, Dr. Eger is uniquely qualified to edit this timely volume.

The book begins with a comprehensive overview of the history and chemistry of nitrous oxide; a few errors in the thermodynamics section detract from the otherwise high quality of these chapters. The review of proposed mechanisms of nitrous oxide analgesia was complete; however, much of the material is controversial, and I found the discussion inconclusive. Dr. Eger's concise chapters on nitrous oxide's MAC and pharmacokinetics are essential reading for trainees and a useful review for practicing anesthesiologists; the concentration effect and gas space expansion principles are especially well explained. The discussion of nitrous oxide delivery systems provided interesting insights into the development of methods for avoiding delivery of hypoxic gas mixtures.

The reviews of cardiovascular and central nervous system effects are, if anything, too extensive: a multitude of sometimes conflicting references made them difficult to follow. In contrast, the sections on nitrous oxide metabolism and interaction with methionine synthetase (with resultant pernicious anemia-like signs) are well-written and appropriately referenced. After a presentation of the laboratory and clinical evidence of the potential risks of chronic, low-level nitrous oxide exposure, there is an excellent review of methods for minimizing and monitoring occupational exposure to waste anesthetic agents.

The work concludes with a unique "point–counterpoint" argument regarding the continued use of nitrous oxide, in light of our increased understanding of its risks and improvements in alternative anesthetics. Dr. Eger explains why a "New Drug Application" for nitrous oxide would probably never be approved: the drug has limited efficacy (must be supplemented to provide surgical anesthesia), must be given in high concentrations (reducing inspired oxygen), has significant harmful effects on the central nervous and hematopoetic systems, and has no unique beneficial properties. Drs. Saidman and Hamilton counter that the benefits of nitrous oxide, rapid uptake and elimination with minimal cardiorespiratory depression, are unique. They emphasize that as with all drugs, "Nitrous oxide should be used only after assessing the reasons for doing so."

Because of its extensive bibliography, *Nitrous Oxide/$N_2O$* is an excellent reference resource, which provides a comprehensive review of the current state of knowledge about this oldest and most ubiquitous of currently used anesthetics.

Jeffrey B. Gross, MD
*Assistant Professor of Anesthesia*
*University of Pennsylvania*
*School of Medicine*
*Philadelphia, PA 19104*

## List of Books Received

Receipt of the following books from their publishers is acknowledged with thanks. Selected books from this list will be reviewed in the future.

Labat's Regional Anesthesia, Techniques and Clinical Applications, 4th edition. J. Adriani. St. Louis: W.H. Green, Inc., 1985, 744 pp, $75.00.

Preoperative Cardiac Dysrhythmias: Mechanism, Recognition, Management. J.L. Atlee III. Chicago: Yearbook Medical Publishers, 1985, 451 pp, $49.95.

Monitoring in Anesthesia and Critical Care Medicine. C.D. Blitt, ed. NY: Churchill Livingstone, Inc., 1985, 740 pp, $79.00.

Regional Anesthesia and Clinical Applications. H. Carron, G.A. Korbon, J.C. Rowlingson. Orlando, FL: Grune & Stratton, 1985, 198 pp, $39.50.

Effects of Anesthesia. B.G. Covino, H.A. Fozzard, K. Rehder, eds. Bethesda, MD: American Physiological Society, 1982, 224 pp, $39.95.

Controlled Hypotension in Neuroanaesthesia. D. Heuser, D.G. McDowall, V. Hempel, eds. NY: Plenum Press, 1985, 230 pp, $35.00.

The Origins of Anesthesia. S.B. Nuland. Birmingham, AL: The Classics of Medicine Library, 1000 pp, $60.00.

Update in Intensive Care and Emergency Medicine. J.L. Vincent, ed. New York, Springer-Verlag, 1985, 304 pp, $31.00.

Precis D'Anesthesie Loco–Regionale. P. Gauthier-Laéfaye. Paris: Masson, 1985, 352 pp, 390 francs.

# Guest Reviewers for 1985

Dr. Hassan H. Ali
Dr. Paul D. Allen
Dr. G. Richard Arthur
Dr. David Ashton
Dr. John L. Atlee
Dr. Paul G. Barash
Dr. Salvatore Basta
Dr. Robert F. Bedford
Dr. Andrew M. S. Black
Dr. Joel C. Bornstein
Dr. Leonard Brand
Dr. Donald C. Brody
Dr. Evan Brown
Dr. Peter Brownridge
Dr. Enrico M. Camporesi
Dr. Norman J. Clark
Dr. Fiona M. Clements
Dr. Peter J. Cohen
Dr. J. G. Collins
Dr. G. M. Cooper
Dr. Kathryn W. Cozine
Dr. Greg Crosby
Dr. Michael C. Damask
Dr. Salha S. Daniel
Dr. Sanjay Datta
Dr. Peter Davis
Dr. Frederick M. deBros
Dr. Norbert P. de Bruijn
Dr. Daniel F. Dedrick
Dr. E. Delphin
Dr. Sukumar P. Desai
Dr. Peter Dwane
Dr. Edmond I. Eger II
Dr. Barry I. Feinberg
Dr. A. D. Fincke
Dr. Mieczyslaw Finster
Dr. I. Fitz-James
Dr. John A. Fox
Dr. Donald N. Franz
Dr. Eric Frisch
Dr. Alex Gallus
Dr. Simon Gelman
Dr. Aaron J. Gissen
Dr. Michael S. Gorback
Dr. Nishan G. Goudsouzian
Dr. Geoffrey K. Gourlay
Dr. William J. Greeley
Dr. Jeffrey B. Gross
Dr. G. Gutteridge
Dr. R. J. Hudson
Dr. Ronald J. Hurley
Dr. Allen I. Hyman
Dr. Anthony H. Ilsley
Dr. Mark Johnson
Dr. R. W. Johnson
Dr. Patricia A. Kapur
Dr. Johannes H. Karis
Dr. Masao Katayama
Dr. Robert A. Kates
Dr. Lee A. Kearse
Dr. Hoshang J. Khambatta
Dr. Igor Kissen
Dr. Luke M. Kitahata
Dr. Greg A. Koski
Dr. Carol L. Lake
Dr. Donald H. Lambert
Dr. Kenneth R. LaMantia
Dr. Carole C. LaMotte
Dr. Demetrios Lappas
Dr. David E. Leith
Dr. I. Lieberman
Dr. Peter E. Lillie
Dr. Edward Lowenstein
Dr. Rosemarie Maddi
Dr. Jonathan B. Mark
Dr. P. Martin
Dr. S. A. Masey
Dr. Laurence E. Mather
Dr. Richard S. Matteo
Dr. G. McLennan
Dr. Ronald M. Meyer
Dr. Hisayo O. Morishima
Dr. Stanley Muravchick
Dr. Craig Nancarrow
Dr. Susan Nicholson
Dr. Tae Hee Oh
Dr. Frederick K. Orkin
Dr. Eugene Ornstein
Dr. Andranik Ovaspassian
Dr. Nathan L. Pace
Dr. Leila Mei Pang
Dr. Hilda Pedersen
Dr. Stan Pietak
Dr. John L. Plummer
Dr. Timothy J. Quill
Dr. Richard K. Raker
Dr. Lloyd F. Redick
Dr. John G. Roberts
Dr. Stanley Rosenbaum
Dr. H. L. Rosner
Dr. Carl E. Rosow
Dr. Robert A. Rush
Dr. W. J. Russell
Professor Michael Sage
Dr. Ernest Salanitre
Dr. Keven V. Sanborn
Dr. A. Santos
Dr. John J. Savarese
Dr. Richard A. Schieber
Dr. Robert C. Schneider
Dr. Alan J. Schwartz
Dr. Derrick G. Selby
Dr. Steve Shelley
Dr. George Skowronski
Dr. Richard A. Steinbrook
Dr. Richard L. Stiller
Dr. Joseph J. Stone
Dr. Guy E. Tanner
Dr. T. A. Thomas
Dr. George P. Topulos
Dr. Lubos Triner
Dr. Alnis E. Vedig
Dr. A. Wald
Dr. Albert Wauquier
Dr. Charles Weissman
Dr. Stephen M. Weitzman
Mr. James Welch
Dr. Dwayne R. Westenskow
Dr. G. G. Whalley
Dr. Richard J. Willis
Dr. John Willoughby
Dr. Roger Wilston
Dr. Margaret Wood

STATEMENT OF OWNERSHIP, MANAGEMENT, AND CIRCULATION (Required by 39 U.S.C. 3685). 1. Title of publication: Anesthesia and Analgesia. B. Publication no.: 00032999. 2. Date of filing: 10/1/85. 3. Frequency of issue: Monthly. A. No. of issues published annually: 12. B. Annual subscription price: $90.00. 4. Location of known office of publication: 52 Vanderbilt Avenue, New York, NY 10017. 5. Location of the headquarters or general business offices of the publishers: 52 Vanderbilt Avenue, New York, NY 10017. 6. Names and complete addresses of publisher, editor, and managing editor: Publisher, International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, OH 44122; Editor, Nicholas M. Greene, MD, Yale University, New Haven, CT 06510. Managing Editor: Susan Tischler, 52 Vanderbilt Avenue, New York, NY 10017. 7. Owner: International Anesthesia Research Society, 3645 Warrensville Center Road, Cleveland, OH 44122. 8. Known bondholders, mortgagees, and other security holders owning or holding 1 percent or more of the total amount of bonds, mortgages, or other securities: None. 9. The purpose, function, and nonprofit status of this organization and the exempt status for Federal income tax purposes have not changed during preceding 12 months. 10. Extent and nature of circulation. A. Total no. copies printed (net press run): Average no. copies each issue during preceding 12 months, 20,628; actual no. copies of single issue published nearest to filing date, 19,751. B. Paid circulation. 1. Sales through dealers and carriers, street vendors, and counter sales: None. 2. Mail subscription: Average no. copies each issue during preceding 12 months, 16,561; actual no. copies of single issue published nearest to filing date 16,830. C. Total paid circulation: Average no. copies each issue during preceding 12 months, 16,561; actual no. copies of single issue published nearest to filing date 16,830. D. Free distribution by mail, carrier or other means, samples, complimentary, and other free copies: Average no. copies each issue during preceding 12 months, 193; actual no. copies of single issue published nearest to filing date, 193. E. Total distribution: Average no. copies each issue during preceding 12 months, 16,754; actual no. copies of single issue published nearest to filing date, 17,023. F. Copies not distributed. 1. Office use, left over, unaccounted, spoiled after printing: Average no. copies each issue during preceding 12 months, 3,874; actual no. copies of single issue published nearest to filing date, 2,728. 2. Return from news agents: None. G. Total: Average no. copies each issue during preceding 12 months, 20,628; actual no. copies of single issue published nearest to filing date, 19,751. 11. I certify that the statements made by me above are correct and complete.

Ed Bonaski
Fulfillment Manager

# Anesthesia and Analgesia

# Annual Index
## Volume 64, 1985

Journal of the International Anesthesia Research Society

# BOARD OF TRUSTEES
## International Anesthesia Research Society

Dean H. Morrow, MD, *Chairman*
Bruce F. Cullen, MD, *Vice Chairman*
Emerson A. Moffitt, MD, *Executive Secretary*
Douglas B. Craig, MD
E. Paul Didier, MD
Judith H. Donegan, MD, PhD
Noel W. Lawson, MD
John T. Martin, MD
Robert K. Stoelting, MD
John L. Waller, MD
Paul R. Dumke, MD, *Emeritus Trustee*
Kenneth K. Keown, MD, *Emeritus Trustee*
Morris J. Nicholson, MD, *Emeritus Trustee*
B. B. Sankey, MD, *Emeritus Trustee*
T. H. Seldon, MD, *Emeritus Trustee*

# EDITORIAL BOARD
## Anesthesia and Analgesia

*Editor in Chief*
Nicholas M. Greene, MD

*Editors*
David R. Bevan, MA, MD, BChir
D. Ryan Cook, MD
Michael J. Cousins, MD, FFARACS, FFARCS
Benjamin G. Covino, MD
Norig Ellison, MD
Mieczyslaw Finster, MD
Allison B. Froese, MD
Edward D. Miller, MD
Daniel M. Philbin, MD
Cedric Prys-Roberts, MA, DM, PhD
J. Gerald Reves, MD
John H. Tinker, MD
K. C. Wong, MD, PhD

*Book Review Editor*
Norig Ellison, MD

ANESTH ANALG
1985;64:1235–48

# Author Index

- Abboud TK, Nagappala S, Murakawa K, David S, Haroutunian S, Zakarian M, Yanagi T, Sheikh-Ol-Eslam A. Comparison of the effects of general and regional anesthesia for cesarean section on neonatalneurologic and adaptive capacity scores 996
  - Sheik-Ol-Eslam A, Yanagi T, Costandi J, Zakarian M, Hoffman D, Murakawa K, Haroutunian S. Safety and efficacy of epinephrine added to bupivacaine for lumbar epidural analgesia in obstetrics 585
  - see Daily PA
- Abi-Nader E, see Bazaral MG
- Abraham E, Markle DR, Fink S, Ehrlich H, Tsang M, Smith M, Meyer A. Continuous measurement of intravascular pH with a fiberoptic sensor 731
- Abraham R, see Matteo RS
- Adams P, Gelman S, Reves JG, Greenblatt DJ, Alvis JM, Bradley E. Midazolam pharmacodynamics and pharmacokinetics in dogs during acute hypovolemia (abstract) 186
- Adenwala J, see Jones MM
- Agoston S, see d'Hollander A
- Albrecht RF, see Van Gorder PN
- Alden MA, see Rector FTR
- Aldrete JA, Hendricks PL. Cost of muscle relaxant drugs (letter) 943
- Ali HH, Basta SJ, Savarese JJ, Gargarian M, Scott RFP, Sunder N, Gionfriddo M. Single twitch and train-of-four responses for atracurium and vecuronium (abstract) 187
  - Savarese J, Basta S, Sunder N, Gionfriddo M, Lineberry C, Batson AG. Does succinylcholine modify the response to atracurium (abstract) 188
  - see Athanasiadis C
  - see de Bros FM
  - see Savarese JJ
  - see Skourtis CT
- Alifimoff JK. 5-Hydroxytryptamine in peripheral reactions (book review) 383
  - Manual of anesthesia (book review) 655
- Allard MW, Cheek DBC. Omission of supplementary potassium perioperatively in cardiac surgery (abstract) 189
- Allen FB, see Chilcoat RT
- Allen M, see Sear J
- Alpert RA, see Roizen MF
- Althaus JS, Beckman JJ, Miller ED Jr. Central serotonin depletion: effect on blood pressure during anesthesia 1163
  - Miller ED, Moscicki JC, Hecker BR, DiFazio CA. Analgetic contribution of sufentanil during halothane anesthesia: a mechanism involving serotonin 857
  - see Miller ED Jr
  - see Stirt JA
- Alvis JM, see Adams P
  - see Menkhaus PG
- Amaha K, see Iwatsuki N
- Amaki Y, Waud BE, Waud DR. Atracurium-receptor kinetics: simple behavior from a mixture 777
  - see Waud BE
- Amoroso M, see Sosis M
- Amory DW, see Sivarajan M
- Andrews DCR, see Fraulini KE
- Angers DG, see Tanner GE
- Anton AH, see Pathak KS
- Aoki M, Kitahata LM, Senami M, Collins JG. Sufentanil: a drug of choice for spinal opioid analgesia as shown in cats (abstract) 190
  - see Senami M
- Apfelbaum JL, see Moss J
- Arai T, see Hatano Y
  - see Umeda S
- Arakawa K, see Goto H
- Arancibia CU, Hawk WD. Unusual complication of a central venous catheter (letter) 92
- Arismendy J, see Rock I
- Aronson HB, see Beilin B
- Artru A, see Glauber D
- Ashton D, Wauquier A. Modulation of a GABA-ergic inhibitory circuit in the in vitro hippocampus by etomidate isomers 975
- Astorga J, see Islas JA
- Athanasiasis C, Skourtis CT, Fahmy NR, Lappas DG, Ali HH. Atracurium in cardiac surgical patients: clinical pharmacology of atracurium in patients undergoing surgery for coronary artery disease (abstract) 191
  - see Skourtis CT
- Atkin DH. Valsalva maneuver in pulmonary artery catheterization (letter) 844
- Auen M, see Nigrovic V
- Avram MJ, Shanks CA, Dykes MHM, Ronai AK, Stiers WM. Statistical methods in anesthesia articles: an evaluation of two American journals during two six-month periods 607
  - see Benzon HT
- Azar I, Thiagarajah S, Lear E. Rapid correction of chronic hypokalemia in dogs (abstract) 192
  - Thiagarajah S, Lear E. The arrhythmogenic dose of epinephrine in chronic hypokalemic dogs (abstract) 193
  - see Krajcirik WJ
  - see Thiagarajah S
- Azuma M, see Osaki S
- Backofen JE, Schauble JF. Hemodynamic changes with prone positioning during general anesthesia (abstract) 194
- Backus WW, see Matteo RS
- Baden JM, Kundomal YR, Luttropp ME Jr, Maze M, Kosek JC. Effects of volatile anesthetics of fentanyl on hepatic function in cirrhotic rats 1183
- Bailey PL, Wilbrink J, Zwanikken P, Pace NL, Stanley TH. Anesthetic induction with fentanyl 48
- Baldwin D, see Sear J
- Balestrieri FJ, Prough DS, Stullken EH, Davis CH Jr, McWhorter JM, Howard G. Hemodynamic events associated with regional anesthesia for carotid endarterectomy 195
- Banner MJ, see Gallagher TJ
  - see Layon AJ
- Banssillon V, see Degoute C-S
- Barabas E, see Korenaga GM
- Baraka A, Muallem M, Baroody M, Mansour R, Sibai AN, Hroun S, Yamut F. Optimization of oxygenation by CPAP during one-lung anesthesia using nitrous oxide: oxygen (letter) 1036
- Barash PG, see Hines RL
  - see Moleski RJ
  - see Tanner GE
- Barber WB, Smith LE, Zaloga GP, Fletcher JR, Cook D, Lake CR, Chernow B. Hemodynamic and plasma catecholamine responses to epinephrine-containing perianal lidocaine anesthesia 924
- Bardeen-Henschel A, see Munshi CA
- Barker RA, see McIntyre AJ
- Barker SJ, Karagianes T. Gastric barotrauma: a case report and theoretical considerations 1026
- Barna CR, see Bashein G
- Barnes PA, see Gallagher TJ
- Barnett WM. Atlas of emergency medicine (book review) 384
- Baroody M, see Baraka A
- Barvais L, see d'Hollander A
- Bashein G, Barna CR. A comprehensive computer system for anesthetic record retrieval 425

Basta JW, see Paulus DA
Basta SJ, see Ali HH
  see Savarese JJ
Bastard OG, see Merin RG
Batson AG, see Ali HH
  see de Bros FM
  see Savarese JJ
Battaglini JW, see Lineberger AS III
Baughman V, see Van Gorder PN
Baumgarten RK. Closed circuit anesthesia is accurate at any altitude (letter) 843
  Humidifiers are unjustified in adult anesthesia (letter) 1224
  Reynolds WJ. Much ado about nothing: trace gaseous metabolites in the closed circuit (letter) 1029
Baurain M, see d'Hollander A
Bazaral MG, Wagner R, Abi-Nader E, Estafanous FG. Comparison of the effects of 15 and 60 μg/kg fentanyl used for induction of anesthesia in patients with coronary artery disease 312
Beattie C, see Stevenson RL
Beaupre P, see Berry AJ
Beckman JJ, see Althaus JS
  see Miller ED Jr
Bedford RF, see Minton MD
Beers PC, see Girard D
Beilin B, Maayan C, Vatashsky E, Shulman D, Vinograd I, Aronson HB. Fentanyl anesthesia in familial dysautonomia 72
Beker B, see Lin CY
Beltran J, see Villalonga A
BenEzra D, see Drenger B
Benefiel DJ, see Roizen MF
Bennett MH, see Ingram MD
Benson KT, see Goto H Benumof JL. One-lung ventilation and hypoxic pulmonary vasoconstriction: implications for anesthetic management 821
  see Rogers SN
Benzon HT, Cheng SC, Avram MJ, Molloy RE. Sign of complete sympathetic blockade: sweat test or sympathogalvanic response? 415
Berger JM, see Nakatsu K
Bernstein KJ, Verosky M, Triner L. Effect of halothane on rat liver adenylate cyclase: role of cytosol components 531
Berry AJ, Isaacson IJ, Kane MA, Schatz GC, Clark BT, Beaupre P, Derrer S, Kapur P, Thompson J, Martin D, Large HS, Maze M, Spiss CK, Ronai AK, Kimovec MA. A multicenter study of the epidemiology of hepatitis B in anesthesia residents 672
  see Weitz FI
Bevan DR. Harold R. Griffith, MD, 1894–1985 (obituary) 945
  see Donati F
Bhalodia R, see Okamoto K
Biehl D, see Kozody R
Bikhazi GB, Flores C, Foldes FF. The effect of verapamil and EGTA on the rat phrenic nerve–hemidiaphragm preparation 505
Binda RE Jr. Understanding anesthesia equipment (book review) 655
Bizzarri DV, see Milliken RA
Blaise G, Roy L. Spinal anesthesia in pediatric surgery (abstract) 196
Blanck TJJ, see Humphrey LS
Blitt CD, see Weldon ST
Block PC. Vent stitch entrapment (letter) 379
Bloor BC, see Flacke JW
Bodily MN, see Meline LJ
Bogard TD, see Dewan DM
Bolsin SN, Gilbe CE. Monitoring the processed EEG (letter) 646; with response by Smith NT, Dec-Silver H, Sanford TJ Jr, Westover CJ Jr, Quinn ML, Klein F, Davis DA 647
Bonica JJ, see Moore DC
Bonnette P, see Fouilladieu JL
Bontempo FA, see Kang YG
Borchardt AC, see Fraulini KE
Borland LM, Roule M, Cook DR. Anesthesia for pediatric orthotopic liver transplantation 117
Boston JR. Computing in anesthesia and intensive care (book review) 183
Botros SB, see Gallagher JD
Bottorff M, see Ramanathan J
Bourke D. Common sense in statistical analyses (letter) 1035; with response by Colliver JA, Manchikanti L
  Counter-irritation reduces pain during cutaneous needle insertion (letter) 379
  see Litwack R
Bove JR. Fresh frozen plasma: too few indications—too much use (editorial) 849
Bradford MW, see Ewart RBL
Bradley E, see Adams P
  see Menkhaus PG
Bradley EL, see Person DL
  see Tverskoy M
Bradley EL Jr, see Ebert J
Brandom BW, Cook DR, Woelfel SK, Rudd GD, Fehr B, Lineberry CG. Atracurium infusion requirements in children during halothane, isoflurane, and narcotic anesthesia 471
  see Stiller RL
Brauer S. Thoughts on protamine toxicity (letter) 1033
  see Royster RL
Braunstein M, see Reitan JA
Braverman B, see El-Ganzouri AR
  see McCarthy RJ
Brizgys RV, see Daily PA
Broadbent MP, see Jones RM
Brocke-Utne JG, see Gregory MA
Bromage PR. Subdural migration of an epidural catheter (letter) 1029
Brookshire GL, see Daily PA
Brotherton WP, see Matteo RS
Brown BR Jr, see Lind RC
Brown KA, Hoffstein V, Byrick RJ. Bedside diagnosis of bilateral diaphragm paralysis in a ventilator-dependent patient after open-heart surgery 1208
Brown PT, see Person DL
Brown RE Jr, see Stirt JA
Brown S, see Lam AM
Bruce DL, Hinkley R, Norman PF. Fentanyl does not inhibit fertilization or early development of sea urchin eggs 498
Bruner JMR. Electric shock injuries in hospitals (letter) 559
Bryan AC, see Tamura M
Buckley FP, Neto GD, Fink BR. Acid and alkaline solutions of local anesthetics: duration of nerve block and tissue pH 477
Bullingham RE, see O'Sullivan GM
Burgess NL, see Silvay G
Burke BC, see Hilgenberg JC
Burns RS, see Lin SK
Bursztein S, see Levin H
Bux S, see Gregory MA
Buzello W, Williams CH, Chandra P, Watkins ML, Dozier SE. Vecuronium and porcine malignant hyperthermia 515
  see Williams CH
Byrick RJ, see Brown KA
Cahalan MK, see Fassoulaki A
  see Roizen MF
Cahill J, see Murphy DF
Caldwell CB, see Gross JB
Callahan DL. Development of resistance to pancuronium in adult respiratory distress syndrome 1126
Campos JH, see Kapur PA
Canella MG, see Manchikanti L
Canfell C, see Shi W-Z
Capuano C, see Liwak B
  see Mazzoni P
Carmichael FJ, Lindop MJ, Farman JV. Anesthesia for hepatic transplantation: cardiovascular and metabolic alterations and their management 108
Carpenter RL, Eger EI II, Johnson BH, Unadkat JD. A new concept in inhaled anesthetic pharmacokinetics (abstract) 197
Carr D, see Fahmy NR
Carr G, see Johans TG
Carter JG, see Merin RG
Cashman JN, see Jones RM
Casson WR, see Jones RM

Cassuto J, Wallin G, Högström S, Faxén A, Rimbäck G. Inhibition of postoperative pain by continuous low-dose intravenous infusion of lidocaine 971
Castagnoli K, see Fisher DM
Chakravorti S, see Stiller RL
Chan KH, see Mok MS
Chan RP, see Roizen MF
Chandra P, see Buzello W
  see Williams CH
Chang J-L, see Rubiano R
Chapin JW, see Ripp CH
Charles DJ, see Gravlee GP
Cheek DBC, see Allard MW
Chelly J, Rogers K, Merin RG, Doursout M-F, Taylor A, Hartley C. Does chronic verapamil (V) treatment affect the cardiovascular effects of anesthetics (abstract) 198
Cheng SC, see Benzon HT
Chernow B, see Barber WB
Cherry KP, see Roizen MF
Chilcoat RT, Gerson JI, Allen FB. Fluosol-DA prolongs induction of isoflurane anesthesia in the dog (abstract) 199
  Gerson JI, Allen FB, Mapleson WW. The effect of fluosol-DA on induction of inhalation anesthesia 405
Child CS, see Hirsch NP
Chraemmer-Jørgensen B, see Leicht P
Chrubasik J, Meynadier J, Scherpereel P, Wunsch E. The effect of epidural somatostatin on postoperative pain 1085
Chubra-Smith NM, Grant RP, Jenkins LC. Transcutaneous oxygen monitoring during endobronchial thoracic anesthesia (abstract) 200
Clark BT, see Berry AJ
Clark DL, see Gallagher JD
Clark WM, see Wang JM
Cohen E, Thys DM, Eisenkraft JB, Kaplan JA. PEEP during one-lung anesthesia improves oxygenation in patients with low arterial $Pa_{O_2}$ (abstract) 201
  see Thys DM
Cohen SE. Epidural blood patch in outpatients: a simpler approach (letter) 458
Colley PS, see Glauber D
Collins C, Koren G, Crean P, Klein J, Roy WL, MacLeod SM. Fentanyl pharmacokinetics and hemodynamic effects in preterm infants during ligation of patent ductus arteriosus 1078
Collins JG, see Aoki M
  see Senami M
  see Yuge O
Colliver JA, see Bourke DL
  see Manchikanti L
Conklin KA, see Murad SHN
Conseiller C, see Fouilladieu JL
Contreras J, see Lam AM
Cook D, see Barber WB
  see Borland LM see Brandom BW
  see Ingram MD
  see Stiller RL
Cook JM, see Van Gorder PN
Cooke RA, see Tierney E
Coombs DW. Potential hazards of transcatheter serial epidural phenol neurolysis 1205
  see Weinlander CM
Cooperman LH. The kidney in anesthesia (book review) 848
Cork RC, Hameroff SR, Weiss JL. Effects of halothane and fentanyl anesthesia on plasma β-endorphin immunoreactivity during cardiac surgery 677
  James MFM. Magnesium pre-treatment at C-section for pregnancy-induced hypertension (abstract) 202
  see Saddler JM
Corssen G, see Trouwborst A
Costandi J, see Abboud TK
Coté CJ, Drop LJ, Daniels AL. Treatment of citrate-induced hypocalcemia in dogs: comparative response to calcium chloride and calcium gluconate (abstract) 203
  Petkau AJ. Thiopental requirements may be increased in children reanesthetized at least one year after recovery from extensive thermal injury 1156
Cottrell JE, see Liwak B
  see Mazzoni P
Courtney JV, see Lichtor JL
Cousins MJ, see Lunam CA
  see Plummer JL
Crandell JT, Kotelko DM. Cardiotoxicity of local anesthetics during late pregnancy (abstract) 204
Crean P, see Collins C
Creel DJ, see Wang JM
Cronnelly R, see Roizen MF
Cross B, see Tremper KK
Curling PE, see Newsome LR
d'Hollander A, Agoston S, Barvais L, Massaut J, Baurain M. Evolution of vecuronium requirements for stable mechanical effect: comparison with or without previous succinylcholine administration 319
Dadabhoy ZP, Tapia DP, Zsigmond EK. Transplacental transfer of nalbuphine in patients undergoing cesarean section (abstract) 205
Dagnino J, Roberts CP. Assessment of β-adrenoceptor blockade during anesthesia in humans: use of isoproterenol dose–response curves 305
Daily PA, Brookshire GL, Shnider SM, Abboud TK, Kotelko DM, Noueihid R, Thigpen JW, Khoo SS, Raya JA, Foutz SE, Brizgys RV, Goebelsmann U, Lo M-W. The effects of naloxone associated with the intrathecal use of morphine in labor 658
  see Roizen MF
Dandekar PV, see Roizen MF
Daniels AL, see Coté CJ
Dauchot PJ, see Lina AA
Dautenhahn DL, see Sheth AP
David S, see Abboud TK
Davidson JT, see Drenger B
Davis CH Jr, see Balestrieri FJ
Davis DA, see Bolsin SN
Davis LJ, see Flacke JW
Davis RF. A comparison of automated oscillometric and catheter–transducer measurements of arterial pressure (abstract) 206
Deamer RL, see Tidyman M
de Bros FM, Lai A, Scott R, de Bros J, Batson AG, Goudsouzian N, Ali HH, Savarese JJ. Pharmacokinetics and pharmacodynamics of atracurium under isoflurane anesthesia in normal and anephric patients (abstract) 207
de Bros J, see de Bros FM
deBruijn N, see Reves JG
Dec-Silver H, see Bolsin SN
Degoute C-S, Saumet J-L, Banssillon V, Dittmar A. Skin blood flow measured by thermal clearance method in anesthesia (letter) 179
de la M Hall P, see Lunam CA
  see Plummer JL
Denis R, see Healy P
DeNuccio DJ, see Rector FTR
Derrer S, see Berry AJ
  see Lina AA
Dewan DM, Floyd HM, Thistlewood JM, Bogard TD, Spielman FJ. Sodium citrate pretreatment in elective cesarean section patients 34
DeWitt DE, see Komai H
Dhasmana KM, see van der Zee HT
Dhingra U, see Rocco AG
DiFazio CA, see Althaus JS
  see Finholt DA
  see Lake CL
Diaz J. Croup and epiglottis in children: the anesthesiologist as diagnostician 621
  see Matteo RS
Didier EP. The B.B. Sankey Anesthesia Advancement Award (editorial) 657
Dimich I, see Griffin RM
Dittmar A, see Degoute C-S
Doddapaneni B, see Douglass R
Dolan DF, see Fiserova-Bergerova V
Donath RW, see Endler GC

Donati F, Bevan DR. Antagonism of phase II succinylcholine block by neostigmine 773
Donchin Y, Feld JM, Porges SW. Respiratory sinus arrhythmia during recovery from isoflurane–nitrous oxide anesthesia 811
Dong M-L. Clinical anesthesia in neurosurgery (book review) 560
Dougal RM, see Lee KWT
Douglass R, Doddapaneni B. Esophageal stethoscope amplifier 377
Doursout M-F, see Chelly J
Downes JJ, see Lee KWT
Downing JW, see Gregory MA
Dozier SE, see Buzello W
  see Williams CH
Drenger B, Peter J, BenEzra D, Katzenelson R, Davidson JT. The effect of intravenous lidocaine on the increase in intraocular pressure induced by tracheal intubation 1211
Drexler H, Zaroura S, Shapira Y. Transient aphonia and quadriplegia during epidural anesthesia 365
Drop LJ. Ionized calcium, the heart, and hemodynamic function 432
  see Coté CJ
Drummond JC, Prutow RJ, Scheller MS. A comparison of the sensitivity of pulmonary artery pressure, end-tidal carbon dioxide, and end-tidal nitrogen in the detection of venous air embolism in the dog 688
  see Todd MM
Dubois M, see Lin SK
Duncalf D, see Nagashima H
Duncan D, see Layon AJ
Dundee JW, Kawar P. Midazolam maleate and hydrochloride (letter) 1223
Durant J, see Martyn JAJ
Durtzman M, see Sheth R
Duvall JO, Griffith DP. Epidural anesthesia for extracorporeal shock wave lithotripsy 544
Dykes MHM, see Avram MJ
Easley S, see Moleski RJ
Ebert J, Malloy C, Laborde P, Proctor J, Bradley EL Jr, Niemann K. Neuroendocrine and hemodynamic responses to induced hypotension during total hip arthroplasty (abstract) 208
  see Varner PD
Edwards MW, see Gross JB
Eger EI, see Shi W-Z
Eger EI II, see Carpenter RL
  see Eger RR
  see Fassoulaki A
  see Fisher NA
  see Lambert DH
  see Lerman J
  see Roizen MF
Eger RR, Eger EI II. Effect of temperature and age on the solubility of enflurane, halothane, isoflurane, and methoxyflurane in human blood 640
  see Fassoulaki A
Ehrlich H, see Abraham E
Eich E, Reeves JL, Katz RL. Anesthesia, amnesia, and the memory/awareness distinction 1143
Eisenkraft JB, see Cohen E
  see Thys DM
Eisler EA, Shapiro DA, Shnider SM, Halpern SH, Levinson G, Rosen MA, Johnson J, Jones MJ. The lethal dose of intravenous bupivacaine with and without epinephrine in rabbits (abstract) 209
El-Ganzouri AR, Ivankovich AD, Braverman B, McCarthy R. Monoamine oxidase inhibitors: should they be discontinued preoperatively? 592
Elixson EM, see Hickey PR
Eltherington LG. Clinical transcutaneous electric nerve stimulation (book review) 848
Endler GC, Donath RW. Inflation device to prevent aortocaval compression during pregnancy 1015
Engle JS, see Lake CL
Epstein JM, see Mazzoni P
Erdmann W, see Trouwborst A
  see van der Zee HT
Ericson HA, Kallen AJB. Hospitalization for miscarriage and delivery outcome among Swedish nurses working in operating rooms 1973–1978 981
Estafanous FG, see Bazaral MG
  see Starr NJ
Ewart RBL, Rusy BF, Bradford MW. Enflurane and adenosine 3′,5′-cyclic monophosphate metabolism in pancreatic islets 18
Fabian JA, Jesudian MC. A simple method for improving the safety of percutaneous cannulation of the internal jugular vein (letter) 1032
Fagraeus L, see Sheth AP
Fahey MR. Use of neurosurgical patients for muscle relaxant studies (letter) 846; with response by Matteo RS
  see Shi W-Z
Fahmy NR, Carr D, Mihelakos P, Lappas DG. Beta endorphin induced hypotension: relation to sympathoadrenal and cardiovascular responses (abstract) 210
  see Athanasiadis C
Fairley HB, see Zinn SE
Faithfull S, see van der Zee HT
Fallacaro MD, see Radel TJ
Fan FC, see Raval RR
Farhi LE, see Plewes JL
Farman JV, see Carmichael FJ
Fassoulaki A, Eger EI II, Johnson BH, Ferrell LD, Smuckler EA, Cahalan MK, Eger RR, Harper MH. Nitrous oxide does not hinder the repair of halothane-induced hepatic injury in the rat 465
Faust RJ, see Messick JM
Faxén A, see Cassuto J
Fehr B, see Brandom BW
Feld JM, see Donchin Y
Feldstein G, Ramanathan S. Obstetrical lumbar epidural anesthesia in patients with previous posterior spinal fusion for kyphoscoliosis 83
Feneck RO, see Waldmann CS
Ferrell LD, see Fassoulaki A
Ferres CJ, see Mirakjur RK
Fine PG. Ordering priorities: improved anesthesia or surgery—the case of cordotomy (letter) 942
Finholt DA, Stirt JA, DiFazio CA. Epidural morphine for postoperative analgesia in pediatric patients (abstract) 211
Fink BR. MAOO versus MAC (letter) 646
  see Buckley FP
Fink S, see Abraham E
Fiserova-Bergerova V, Dolan DF. Transient inhibitory effect of isoflurane upon oxidative halothane metabolism 1171
Fisher DM, Castagnoli K, Miller RD. Pharmacokinetics and pharmacodynamics of vecuronium in anesthetized infants and children (abstract) 212
  see Shi W-Z
Fisher NA, Iwata RT, Eger EI II, Smuckler EA. Hepatic necrosis associated with herpes virus after isoflurane anesthesia 1131
Fitz-James I, see Tamura M
Fitzpatrick G, see Murphy DF
Flacke JW, Bloor BC, Kripke BJ, Flacke WE, Warneck CM, Van Etten AP, Wong DH, Katz RL. Comparison of morphine, meperidine, fentanyl, and sufentanil in balanced anesthesia: a double-blind study 897
  Davis LJ, Flacke WE, Bloor BC, Van Etten AP. Effects of fentanyl and diazepam in dogs deprived of autonomic tone 1053
Flacke WE, see Flacke JW
Fletcher JR, see Barber WB
Flicker S, see Gallagher JD
Flores C, see Bikhazi GB
Floyd HM, see Dewan DM
Foldes FF, see Bikhazi GB
  see Gallant EM
  see Nagashima H
Foster S. Relating knowledge and clinical competency skills (letter) 90; with response by Miller EV 91
Fouilladieu JL, Hosanski M, McGee K,

Korvin M, Bonnette P, Joulin Y, Conseiller C. Possible potentiation by hydroxyzine of metoclopramide's undesirable side effects (letter) 1227
Foultz SE, see Daily PA
  see Rosen MA
Fowler KC, see Tverskoy M
Fox DF, see Goto H
Fraulini KE, Borchardt AC, Andrews DCR, Slaymaker F. Mean body temperature of recovery room adults (abstract) 213
Frazer BM, see Roizen MF
Freiberger D, see Rocco AG
Friesen RH. Pulse oximetry during pulmonary artery surgery 376
Fromme GA, Gray JR. A comparison of intrathecal and epidural morphine for treatment of post-thoracotomy pain (abstract) 214
Fujimori M, see Yukioka H
Fulfer RT, see Williams CH
Fung H-L, see Lichtenthal PR
Furumido H, see Yamamura T
Gaba D, Maze M, Metz S, Smith C, Henderson V, Miller C. Adrenergic function during cardiopulmonary bypass in the dog (abstract) 215
  Metz S, Maze M. Adrenergic or calcium blockade does not prevent post-countershock myocardial damage in halothane anesthetized dogs 216
  see Hayward E
Gallagher JD, Moore RA, Kerns D, Jose AB, Botros SB, Flicker S, Naidech H, Clark DL. Effects of colloid or crystalloid administration on pulmonary extravascular water in the postoperative period after coronary artery bypass grafting 753
Gallagher TJ, Banner MJ, Barnes PA. Large volume crystalloid resuscitation does not increase extravascular lung water 323
  see Griffeth JK
  see Layon AJ
Gallant EM, Foldes FF, Rempel WE, Gronert GA. Verapamil is not a therapeutic adjunct to dantrolene in porcine malignant hyperthermia 601
Galloway PA, Glass PSA. Anesthetic implications of prolonged QT interval syndromes 612
Gandolfi AJ, see Lind RC
  see Weldon ST
Gargarian M, see Ali H
  see Savarese JJ
Garry B, see Hammer M
Gehrke CW, see Williams CH
Gelb AW, see Manninen PH
Gelman S. Hypocarbia and myocardial circulation (letter) 462
  see Adams P
  see Tverskoy M
Gencarelli PJ, see Swen J
Gerhardt KO, see Williams CH
Gerson JI, see Chilcoat RT
Ghia JN, see Levy JH
Gibson FM, see Lavery GG
  see Mirakjur RK
Giese JL, Stockham RJ, Stanley TH, Pace NL, Nelissen RH. Etomidate versus thiopental for induction of anesthesia 871
Giffin JP, see Liwak B
  see Mazzoni P
Gilbe CE, see Bolsin SN
Gillman MA. Anesthesia and analgesia are mediated by different mechanisms (letter) 752; with response by Ueda I, Kamaya H
Gillmor ST, see Stockham RJ
Gionfriddo M, see Ali H
  see Savarese JJ
Girard D, Thys DM, Kaplan JA, Mindich BP, Beers PC, Mikula SK. Hemodynamic effects of esmolol during fentanyl anesthesia for CABG (abstract) 217
  see Silvay G
Glass PSA, see Galloway PA
Glass RH, see Roizen MF
Glasser SA, see Sosis M
Glauber D, Colley PS, Haschke R, Artru A. Blood histamine levels during trimethaphan-induced hypotension (abstract) 218
Glenn JD, see Zinn SE
Goebelsmann U, see Daily PA
Goetzl EJ, see Roizen MF
Goldberg M, Jacoby JJ. A substitute for 4% cocaine (letter) 457
  Michail S, Niswander D. An unusual source of error of cardiac output measurement (letter) 652
Goldman M, see Hillel Z
  see Thys D
Gomar C, see Villalonga A
Gordon L, Wood AJJ, Wood M. Acute effects of halothane on drug distribution in the dog (abstract) 219
Goto H, Kushihashi T, Benson KT, Kato H, Fox DF, Arakawa K. Heparin, protamine, and ionized calcium in vitro and in vivo 1081
Gotoh Y, see Osaki S
Goudsouzian NG, Smith B. Atracurium infusion in children anesthetized with halothane, enflurane and $N_2O/O_2$ narcotics (abstract) 220
  see de Bros FM
  see Martyn JAJ
Govier AV, see Menkhaus PG
Grant RP, see Chubra-Smith NM
Gravlee GP, Wong AB, Charles DJ. Hypoxemia during cardiopulmonary bypass from leaks in the gas supply system (letter) 649
  see Royster RL
Gray JR, see Fromme GA
Grayson R, see Toung TJK
Greenblatt DJ, see Adams P
Greene NM. Distribution of local anesthetic solutions within the subarachnoid space 715
Greene SJ, Shanks CA, Ronai AK, Ramseur A. Atracurium-induced neuromuscular blockade in five myasthenic patients (abstract) 221
Gregory GA, see Lerman J
Gregory MA, Brocke-Utne JG, Bux S, Downing JW. Morphine concentration in brain and spinal cord after subarachnoid morphine injection in baboons 929
Griffeth JK, Packer DL, Gallagher TJ. The effect of nifedipine on aspiration in dogs (abstract) 222
Griffin RM, Dimich I, Pratilas V, Jurado R, Kaplan JA. Cardiovascular effects of diltiazem infusion during fentanyl anesthesia (abstract) 223
  see Wojtczak JA
Griffith DP, see Duvall JO
Groen F, see Stockham RJ
Gronert GA, see Gallant EM
  see Roth JL
Gross JB, Caldwell CB, Edwards MW. Induction dose–response curves for midazolam and ketamine in premedicated ASA class III and IV patients 795
  Edwards MW, Caldwell CB. Dose–response curves for midazolam induction in premedicated ASA PS III and IV patients (abstract) 224
  Nitrous oxide/$N_2O$ (book review) 1230
Grow JB, see Manchikanti L
Guffin AV, see Kaplan JA
Guzman F, see Van Gorder PN
Hadley CH, see Manchikanti L
Hagen JF, see Pinchak AC
Hain WR, see Tierney E
Hall F, see Pinchak AC
Halpern SH, see Eisler EA
Ham J, Redpath JH. Comparative monitoring of non-depolarizing neuromuscular blockade in humans (abstract) 225
  Redpath JH. Respiratory effects of atracurium in humans (abstract) 226
Hambro K, see Morita S
Hameroff SR, see Cork RC
Hammer M, Garry B. Transillumination of the trachea with flexilum (letter) 91
Hand C, see Sear J
Hansen DD, see Hickey PR
Harinck-de Weerd J, see van der Starre PJA
Haroutunian S, see Abboud TK
Harper MH, see Fassoulaki A

Hartley C, see Chelly J
Hartrick CT, Pither CE, Pai U, Raj P, Tomsick TA. Subdural migration of an epidural catheter 175
Hartung J, see Mazzoni P
Hartzell CR, Johnson GVW. In vivo MAC values and in vitro experimentation 386
  see Johnson GVW
Haschke R, see Glauber D
Hatano Y, Arai T, Komatsu K, Kabayama Y. Ventilatory management of massive bronchial hemorrhage by endobronchial high-frequency jet ventilation and continuous suctioning 742
Hawk WD, see Arancibia CU
Haworth C, see Minton MD
Hayward E, Metz S, Gaba D, Smith CS, Spiss C, Maze M. $\alpha_1$Blockade by droperidol raises the threshold for halothane–epinephrine arrhythmias in dogs (abstract) 227
Healy P, Rao TLK. Psychomotor tests and "street fitness" (letter) 182; with response by Denis R, Letourneau J, Londorf D
Heaver JE, see Rosenberg PH
Hecker BR, see Althaus JS
Heifetz M, see Levin H
Helgesen KG, see Hotvedt R
Hellman JH, see Matjasko MJ
Helrich M, see Matjasko MJ
Henderson V, see Gaba D
Hendricks PL, see Aldrete JA
Henling CE, see Menkhaus PG
Hickey PR, Hansen DD, Wessel DL, Lang P, Jonas RA. Pulmonary and systemic hemodynamic responses to fentanyl in infants 483
  Hansen DD, Wessel DL, Lang P, Jonas RA, Elixson EM. Blunting of stress responses in the pulmonary circulation of infants by fentanyl 1137
Hilgenberg JC, Burke BC. Positive end-expiratory pressure produced by water in the condensation chamber of a $CO_2$ absorber 541
Hill AB, Muller BJ, Samra S, Kirsh M. The hemodynamic effects of lorazepam as an adjunct to fentanyl/oxygen anesthesia (abstract) 228
Hillel Z, Thys D, Goldman M, Mindich B, Kaplan JA. 2-D ECHO study of LV mechanics in CABG patients receiving nitroprusside (abstract) 229
  see Thys D
Hillman DE, see Wang BC
Hines RL, Barash PG. Protamine: does it alter right ventricular performance? (abstract) 230
Hinkle AJ, Serum inorganic fluoride post-enflurane in children (abstract) 231
Hinkley R, see Bruce DL
Hinkley RE Jr, Wright BD. Comparative effects of halothane, enflurane, and methoxyflurane on the incidence of abnormal development using sea urchin gametes as an in vitro model system 1005
Hirsch NP, Child CS, Wijetilleka SA. Paraplegia caused by spinal angioma—possible association with epidural analgesia 937
Hoffman BB, see Spiss CK
Hoffman D, see Abboud TK
Hoffman WE, see Van Gorder PN
Hoffstein V, see Brown KA
Högström S, see Cassuto J
Holtackers TR, see McMichan JC
Horrow JC. Protamine: a review of its toxicity 348
Hosanski M, see Fouilladieu JL
Hotvedt R, Refsum H, Helgesen KG. Cardiac electrophysiologic and hemodynamic effects related to plasma levels of bupivacaine in the dog 388
Howard G, see Balestrieri FJ
Howie MB, McSweeney TD, Lingam RP, Maschke SP. A comparison of fentanyl–$O_2$ and sufentanil–$O_2$ for cardiac anesthesia 877
Hroun S, see Baraka A
Hubbert CH. Epidural anesthesia in patients with spinal fusion (letter) 843
Hudson RJ. Significant differences (letter) 559
Hufstedler SM, see Tremper KK
Hug CC Jr, see Newsome LR
Humphrey LS, Blanck TJJ. Intraoperative use of verapamil for nitroglycerin-refractory myocardial ischemia 68
Hunniset A, see Sear J
Hwong BF, see Mok MS
Hymes JA. Seizure activity during isoflurane anesthesia 367
  see Keats AS
Ilias WK, see Williams CH
Imrie DD, see McIntyre AJ
Ingram MD, Sclabassi RJ, Stiller RL, Cook DR, Bennett MH. Cardiovascular and electroencephalographic effects of laudanosine in "nephrectomized" cats (abstract) 232
Isaacson IJ, see Berry AJ
Islas JA, Astorga J, Laredo M. Epidural ketamine for control of postoperative pain 1161
  see Levy JH
Ivankovich AD, see El-Ganzouri AR
  see McCarthy RJ
Iwasaki H, Namiki A, Omote K, Omote T, Takahashi T. Response differences of paretic and healthy extremities to pancuronium and neostigmine in hemiplegic patients 864
Iwata RT, see Fisher NA
Iwatsuki N, Katoh M, Ono K, Amaha K. Antiarrhythmic effect of diltiazem during halothane anesthesia in dogs and in humans 964
Jacobs HK, Lim S, Salem MR, Rao TLK, Mathru M, Smith BD. Cardiac electrophysiologic effects of pancuronium 693
Jacobson RC, see Stevenson RL
Jacoby JJ, see Goldberg ME
James MFM, see Cork RC
  see Saddler JM
Jantzen J-PAH. Tracheal intubation—blind but not mute (letter) 651
Jelenich S, see Lawson D
Jenkins LC, see Chubra-Smith NM
Jenner MA, see Plummer JL
Jesudian MC, see Fabian JA
Johans TG, Carr G. Peripheral nerve stimulation through a local anesthetic path: a modified Koons technique 1217
Johnson BH, see Carpenter RL
  see Fassoulaki A
Johnson GVW, Hartzell CR. Choline uptake, acetylcholine synthesis and release, and halothane effects in synaptosomes 395
  see Hartzell CR
Johnson J, see Eisler EA
Johnston WE, see Royster RL
Jonas RA, see Hickey PR
Jones JE, see Means LJ
Jones MJ, see Eisler EA
Jones MM, Joyce TH, Adenwala J, Mawji F. Comparison of thiopental–nitrous oxide–halothane with ketamine–oxygen–halothane as anesthetic agents for cesarean section (abstract) 233
Jones RM, Cashman JN, Casson WR, Broadbent MP. Verapamil potentiation of neuromuscular blockade: failure of reversal with neostigmine but prompt reversal with edrophonium 1021
Jose AB, see Gallagher JD
Joseph MM, Win KK, Nelson DH, Warner DL, Steen SN. Mask induction responses to a pre-determined technique and recovery characteristics of isoflurane anesthesia in children (abstract) 234
Joulin Y, see Fouilladieu JL
Joyce TH, see Jones MM
Jurado R, see Griffin RM
Kabayama Y, see Hatano Y
Kalish MA. Be aware and read (letter) 179
Kalla GN. Safety for anesthesiologists (letter) 93
Källén AJB, see Ericson HA
Kamaya H, see Gillman MA

Kane MA, see Berry AJ
Kang YG, Martin DJ, Marquez J, Lewis JH, Bontempo FA, Shaw BW, Starzl TE, Winter PM. Intraoperative changes in blood coagulation and thromboelastographic monitoring in liver transplantation 888
Kanno M, see Osaki S
Kaplan JA, Guffin AV. Shivering and changes in mixed oxygen saturation after cardiac surgery (abstract) 235
  see Cohen E
  see Girard D
  see Griffin RM
  see Hillel Z
  see Silvay G
  see Thys D
  see Wojtczak JA
Kaplan R, see Nagashima H
Kapur P, Tippit SE, Campos JH. Influence of diltiazem on myocardial metabolism and coronary hemodynamics during isoflurane anesthesia in the dog (abstract) 236
  see Berry AJ
  see Murad SHN
Karagianes T, see Barker SJ
Karasek J. Narcotics and the sphincter of Oddi (letter) 379; with response by McCammon RL, Stoelting RK, Madura JA 380
Kasten GW, Martin ST. Bupivacaine cardiovascular toxicity: comparison of treatment with bretylium and lidocaine 911
  Martin ST. Successful cardiovascular resuscitation after massive intravenous bupivacaine overdosage in anesthetized dogs 491
Kates RA, see Reves JG
Kato H, see Goto H
Katoh M, see Iwatsuki N
Katz RL, see Eich E
  see Flacke JW
Katzenelson R, see Drenger B
Kaufman RD, see Neubauer KR
Kawano T, see Tamura M
Kawar P, see Dundee JW
Keane JF, see Lam AM
Keats AS. Seizures from isoflurane? (letter) 1225; with response by Hymes JA 1226
Kehrberger E, see Lanz E
Kennard MJ, see Kuhnert BR
Kerns D, see Gallagher JD
Khoo SS, see Daily PA
Kilpatrick DS, see Wangler MA
Kim J-M, Kovac AL, Mathewson HS. A method for detection of incompetent unidirectional dome valves: a prevalent malfunction 745
  Kovac AL, Mathewson HS. Incompetency of unidirectional dome calves: a multi-hospital study (abstract) 237
Kim SJ, see Park WY
Kim YD, Nematzadeh D, Lees DE, Wolf PH, Rose JC, Kot PA, Macnamara TE. Halothane effects on subendocardial oxygen supply–demand balance: estimation from intramyocardial tissue pressure and left ventricular pressure, 1149
Kimball RS, see Rector FTR
Kimovec MA, see Berry AJ
King H-K. Translaryngeal guided intubation (letter) 650
King K, see Stockham RJ
Kinley CE, see McIntyre AJ
Kinzer JB, Lichtenthal PR, Wade LD. Loss of radial artery pressure trace during internal mammary artery dissection for coronary artery bypass graft surgery 1134
Kirby RR. The year book of critical care medicine (book review) 654
Kirkpatrick A, see Korenaga GM
Kirsh M, see Hill AB
Kiskis AA, see Lerman J
Kissin I, see Menkhaus PG
  see Person DL
Kitahata LM, see Aoki M
  see Senami M
  see Yuge O
Klein F, see Bolsin SN
Klein J, see Collins C
Klie H, see Paulus DA
Klowden AJ. Endocrinology and the anaesthetist (book review) 1039
Koch F. Manual of cardiac anesthesia (book review) 560
Koht A, see Sloan T
Koike M, see Rosen MA
Komai H, DeWitt DE, Rusy BF. Negative inotropic effect of etomidate in rabbit papillary muscle 400
Komatsu K, see Hatano Y
Komatsu T, see Okamoto K
Koot HWJ, see Swen J
Koren G, see Collins C
Korenaga GM, Kirkpatrick A, Lord JG, Barabas E, Winnie AP, Zsigmond EK. Effect of esmolol on tachycardia induced by endotracheal intubation (abstract) 238
Korttila K, Valanne J. Recovery after outpatient isoflurane and enflurane anesthesia (abstract) 239
Korvin M, see Fouilladieu JL
Kosek JC, see Baden JM
Kot PA, see Kim YD
Kotelko DM, see Crandell JT
  see Daily PA
Kovac AL, see Kim J-M
Kozody R, Swartz J, Palahniuk RJ, Biehl D, Wade JG. Spinal cord blood flow following subarachnoid lidocaine (abstract) 240
Krajcirik WJ, Azar I, Opperman S, Lear E. Anesthetic management of a patient with Moebius syndrome 371
Krieger W, Laxer KD. Seizures with etomidate anesthesia (letter) 1226
Kripke BJ, see Flacke JW
Kroll DA, see Samra SK
Kubal K, see Okamoto K
Kuhnert BR, Linn PL. The effect of chloroprocaine on neonatal neurobehavior (letter) 1223
  Linn PL, Kennard MJ, Kuhnert PM. Effects of low doses of meperidine on neonatal behavior 335
Kuhnert PM, see Kuhnert BR
Kundomal YR, see Baden JM
Kushihashi T, see Goto H
Kuypers MH, see van der Zee HT
LaFontaine E, see Lin CY
Laborde P, see Ebert J
Lai A, see de Bros FM
Lake CL. A practice of anaesthesia (book review) 655
  DiFazio CA, Moscicki JC, Engle JS. Reduction in halothane MAC: comparison of morphine and fentanil (abstract) 241
  DiFazio CA, Moscicki JC, Engle JS. Reduction sinus arrhythmia during recovery from isoflurane–nitrous oxide anesthesia 811
Lake CR, see Barber WB
Lalka SA, see Lina AA
Lam AM, Contreras J, Keane JF, Manninen PH, Brown S. Effects of mild hypothermia on brain stem auditory and somatosensory evoked responses (abstract) 242
  see Manninen PH
Lambert DH. Isoflurane and hepatic dysfunction (letter) 458; with response by McLaughlin DF, Eger EI II 459
Lampe GH, see Roizen MF
Landymore R, see McIntyre AJ
Lang P, see Hickey PR
Lanz E, Kehrberger E, Theiss D. Epidural morphine: a clinical double-blind study of dosage 786
  see Murphy DF
Lappas DG, see Athanasiadis C
  see Fahmy NR
  see Skourtis CT
Laredo M, see Islas JA
Large HS, see Berry AJ
Larson CE, see Rubiano R
Larson MD. Surgically induced hypertension in brain dead patients (letter) 1030
Latta W, see Morita S
Laughlin TP, Newberg LA. Prolonged myoclonus after etomidate anesthesia 80

Lavery GG, Mirakhur RK, Gibson FM. A comparison of edrophonium and neostigmine for the antagonism of atracurium-induced neuromuscular block 867

Lawler RA, see Rubiano R

Lawson D, Jelenich S. Capnographs: a new operating room pollution hazard? (letter) 378

Laxenaire MC, see Moneret-Vautrin DA

Laxer KD, see Krieger W

Layon AJ, Duncan D, Gallagher TJ, Banner MJ. Effects of hypertonic saline on extravascular lung water of sheep in hemorrhagic shock (abstract) 243

Lear E, see Azar I
  see Krajcirik WJ
  see Thiagarajah S

Lee C, see Murad SHN

Lee KWT, Dougal RM, Templeton JJ, Downes JJ. Tracheal gas leak and intraoperative tracheal aspiration in children (abstract) 244

Lee S, see Nagashima H

Lee V, see Tremper KK
  see Lin SK

Lees DE, see Kim YD

Leicht P, Wisborg T, Chraemmer-Jørgensen B. Does intravenous lidocaine prevent laryngospasm after extubation in children? 1193

Lell WA. Cardiovascular anesthesia (book review) 1039
  see Menkhaus PG

Lenggenhager K. Treatment of severe bronchial asthma with a low-pressure chamber and 100% $O_2$ 551

Lennon RL. The 2-chloroprocaine test for axillary brachial plexus (letter) 646

Lerman J, Gregory GA, Willis MM, Schmitt BI, Eger EI II. Age and the solubility of volatile anesthetics in ovine tissues 1097
  Kiskis AA. Effects of intravenous lidocaine and high-dose pancuronium on intraocular pressure in children (abstract) 245

Letourneau J, see Healy P

Levin H, Bursztein S, Heifetz M. Cardiac arrest in a child with an anterior mediastinal mass 1129

Levinson G, see Eisler EA
  see Rosen MA

Levy JH. Anaphylaxis to chymopapain after antihistamine pretreatment (letter) 90
  Islas JA, Ghia JN, Turnbull C. A retrospective study of the incidence and causes of failed spinal anesthetics in a university hospital 705
  see Weitz FI

Lewis JH, see Kang YG

Lichtenthal PR, Rossi EC, Louis G, Rehnberg KA, Wade LD, Michaelis LL, Fung H-L, Patrignani P. Dose-related prolongation of the bleeding time by intravenous nitroglycerin 30
  see Kinzer JB

Lichtor JL, Little AG, MacMahon H, Courtney JV. Flow versus volume postoperative breathing devices (abstract) 246

Lim S, see Jacobs HK

Lin CY, Beker B, LaFontaine E. Accuracy of radial artery pressure monitoring (abstract) 247

Lin SK, Tremper KK. Clearance from cerebrospinal fluid of intrathecally administrered $\beta$-endorphin in monkeys (letter) 180; with response by Lee VC, Dubois M, Burns RS 181

Lina AA, Rhodes RS, Dauchot PJ, Derrer S, Lalka SA. Potentiation of verapamil-induced cardiovascular depression by propranolol in anesthetized dogs (abstract) 248

Lind RC, Gandolfi AJ, Sipes IG, Brown BR Jr. Comparison of requirements for hepatic injury with halothane and enflurane in rats 955

Lindop MJ, see Carmichael FJ

Lineberger AS III, Sprague DH, Battaglini JW. Sinus arrest associated with cimetidine 453, 554

Lineberry C, see Ali HH
  see Brandom BW

Lingham RP, see Howey MB

Linn PL, see Kuhnert BR

Lippmann M, see Mok MS

Litt L, see Roizen MF

Little AG, see Lichtor JL

Litwack R, Bourke D. A complication caused by an adhesive plastic drape (letter) 462

Liwak B, Giffin JP, Cottrell JE, Capuano C, Stein C. Intracranial pressure after atracurium in cats (abstract) 249

Lo M-W, see Daily PA

Londorf D, see Healy P

Longnecker DE, see Weinberg G

Lord JG, see Korenaga GM

Louie BW, see Mok MS

Louis G, see Lichtenthal PR

Lumley J, Morgan M. Myoclonus after etomidate anesthesia (letter) 1034

Lunam CA, Cousins MJ, de la M Hall P. Halothane hepatotoxicity (HH) in a guinea pig (G-P) model in the absence of conditioning factors (abstract) 250

Luttropp ME Jr, see Baden JM

Ma C, see Murad SHN

Maayan C, see Beilin B

Mac N, see Tidyman M

MacEvilly M, see Murphy DF

MacKenzie CF, see Matjasko MJ

MacKenzie NL, see Roizen MF

MacLeod SM, see Collins C

MacMahon H, see Lichtor JL

Macnamara TE, see Kim YD
  see Park WY

Madura JA, see Karasek K

Malarik P, see Sommer RM

Malloy C, see Ebert J

Manchikanti L, Colliver JA, Marrera TC, Roush JR. Assessment of age-related acid aspiration risk factors in pediatric, adult, and geriatric patients 11
  Grow JB, Colliver JA, Canella MG, Hadley CH. Atracurium pretreatment for succinylcholine-induced fasciculations and postoperative myalgia 1010
  see Bourke DL

Manninen PH, Lam AM, Gelb AW. The effect of isoflurane induced hypotension on the myocardium (abstract) 251
  Lam AM, Nicholas JF. The effects of isoflurane and isoflurane–nitrous oxide anesthesia on brainstem auditory evoked potentials in humans 43
  see Lam AM

Mansour R, see Baraka A

Mapleson WW, see Chilcoat RT

Markle DR, see Abraham E

Marquez J, see Kang YG

Marrero TC, see Manchikanti L

Martin D, see Berry AJ
  see Kang YG

Martin ST, see Kasten GW

Martyn JAJ, Durant J, Szyfelbein SK, Goudsouzian NG. Cardiovascular and pharmacodynamic effects of high dose pancuronium–metocurine combination (abstract) 252

Maschke SP, see Howey MB

Massaut J, see d'Hollander A

Mathewson HS, see Kim J-M

Mathru M, see Jacobs HK

Matjasko MJ, Hellman JH, Mackenzie CF, Helrich M. The sensitivity of end-tidal nitrogen in the detection of large bolus venous air embolism in dogs (abstract) 253

Matsumoto M, see Yuge O

Matteo RS, Backus WW, McDaniel DD, Brotherton WP, Abraham R, Diaz J. Pharmacokinetics and pharmacodynamics of *d*-tubocurarine and metocurine in the elderly 23
  see Fahey MR
  see Shayevitz JR

Mawji F, see Jones MM
Maze M, see Baden JM
  see Berry AJ
  see Gaba D
  see Hayward E
  see Spiss CK
Mazzoni P, Giffin JP, Cottrell JE, Hartung J, Capuano C, Epstein JM. Intracranial pressure during diltiazem-induced hypotension in anesthetized dogs 1001
McCammon RL, see Karasek J
McCarthy R, Braverman B, Ivankovich AD. Comparison of fentanyl and vasopressor responses in chronic dogs on imipramine vs tranylcypromine (abstract) 254
  see El-Ganzouri AR
McDaniel DD, see Matteo RS
McDermott DJ, see Moss J
McGee K, see Fouilladieu JL
McIntyre AJ, Moffitt EA, Barker RA, Imrie DD, Murphy DA, Landymore R, Kinley CE. Myocardial metabolism and hemodynamic responses with fentanyl–enflurane anesthesia in coronary patients (abstract) 255
McKay RD, see Varner PD
McKenzie SM, see Sivarajan M
McLaughlin DF, see Lambert DH
McMichan JC, Oliver WC, Holtackers TR, Pairolero P. Transcutaneous electrical nerve stimulation (TENS) for the relief of pain following thoracotomy (abstract) 256
McQuay H, see Sear J
McSweeney TD, see Howey MB
McWhorter JM, see Balestrieri FJ
Means LJ, Jones JE, Rao CC. Sublingual emphysema complicating dental anesthesia 737
Meline LJ, Westenskow DR, Pace NL, Bodily MN. Computer-controlled regulation of sodium nitroprusside infusion 38
Menkhaus PG, Reves JG, Kissin I, Alvis JM, Govier AV, Samuelson PN, Lell WA, Henling CE, Bradley E. Cardiovascular effects of esmolol in anesthetized humans 327
Merin RG. Importance of anesthetic equivalence (letter) 381; with response by Bastard OG, Moyers JR, Carter JG
  see Chelly J
Messick JM, Newberg LA, Nugent M, Faust RJ. Principles of neuroanesthesia for the nonneurosurgical patient with CNS pathophysiology 143
Metz S, see Gaba D
  see Hayward E
Meyer A, see Abraham E
Meynadier J, see Chrubasik J
Michaelis LL, see Lichtenthal PR
Michail S, see Goldberg M
Mihelakos P, see Fahmy NR
  see Skourtis CT
Mikula SK, see Girard D
Miletich DJ, see Van Gorder PN
Miller C, see Gaba D
Miller ED, see Althaus JS
Miller ED Jr, Beckman JJ, Althaus JS. Hormonal and hemodynamic responses to halothane and enflurane in spontaneously hypertensive rats 136
  see Althaus JS
Miller EV, see Foster S
Miller J, see Price DD
Miller PL, see Tanner GE
Miller RD, see Fisher DM
  see Shi W-Z
Milliken RA, Bizzarri DV. Flammable surgical drapes—a patient and personnel hazard 54
Mindich B, see Girard D
  see Hillel Z
  see Silvay G
  see Thys D
Ming-de W, Zhen-Lin R. Aminophylline antagonism of the residual effects of fentanyl anesthesia (letter) 1034
Minton MD, Stirt JA, Bedford RF. Atracurium and intracranial pressure in man (abstract) 257
  Stirt JA, Bedford RF, Haworth C. Intracranial pressure after atracurium in neurosurgical patients 1113
Mirakjur RK, Gibson FM, Ferres CJ. Vecuronium and *d*-tubocurarine combination: potentiation of effect 711
  see Lavery GG
Moffitt EA, see McIntyre AJ
Mok MS, Louie BW, Hwong BF, Chan KH, Lippmann M. Epidural nalbuphine for the relief of pain after thoracic surgery (abstract) 258
Moldenhauer CC, see Newsome LR
Moleski RJ, Easley S, Barash PG, Primer G, Shier NQ, Schrier RI. Control and accountability of controlled substance administration in the operating room 989
Molloy RE, see Benzon HT
Moneret-Vautrin DA, Laxenaire MC. Anaphylactoid reaction to pancuronium (letter) 944
Moore A, see Sear J
Moore DC, Bonica JJ. Convulsions and ventricular tachycardia from bupivacaine with epinephrine: successful resuscitation—congratulations! (letter) 844
Moore DG. Saline with benzyl alcohol prevents pain of needle insertion: true but dangerous (letter) 559
Moore RA, see Gallagher JD
Morgan M, see Lumley J
Morita S, Latta W, Hambro K, Snider MT. Accumulation of methane, acetone, and nitrogen in the inspired gas during closed-circuit anesthesia 343
Morris P, see Sear J
Moscicki JC, see Althaus JS
  see Lake CL
Moss J, Roizen MF, Nordby EJ, Thisted R, Apfelbaum JL, McDermott DJ. Decreased incidence and mortality of anaphylaxis to chymopapain 1197
Motoyama EK, see Tyler IL
Moyers JR, see Merin RG
Muallem M, see Baraka A
Mulla A, see Tanner GE
Muller BJ, see Hill AB
Munshi CA. Bardeen-Henschel A. Hydropneumothorax after percutaneous nephrolithotomy 840
Munson ES. Subjective evaluation of anesthesia textbooks: relation to currency 362
Murad SHN, Tabsh KMA, Shilyanski G, Kapur PA, Ma C, Lee C, Conklin KA. Effects of verapamil on uterine blood flow and maternal cardiovascular function in the awake pregnant ewe 7
Murakawa K, see Abboud TK
Murphy DA, see McIntyre AJ
Murphy DF. Anesthesia and intraocular pressure 520
  Cahill J, Fitzpatrick G, MacEvilly M. Epidural buprenorphine for postoperative pain relief (letter) 456; with response by Lanz E, Theiss D 457
Murray E, see Rocco AG
Nagano M, see Shigematsu T
Nagappala S, see Abboud TK
Nagashima H, Nguyen HD, Lee S, Kaplan R, Foldes FF, Duncalf D. The combined use of atracurium and pancuronium for the production of surgical relaxation (abstract) 259
Nagle DM, see Newsome LR
Naidech H, see Gallagher JD
Nail CS, see Varner PD
Nakatsu K. Anesthetics and theophylline metabolism (letter) 460; with response by Berger JM, Stirt JA, Sullivan SF 461
Nakaya H, see Osaki S
Nalda MA, see Villalonga A
Namiki A, see Iwasaki H
Naulty JS, see Sinatra RS
  see Weintraub SJ
Nelissen RH, see Giese JL

Nelson DH, see Joseph MM
Nelson TE, see Suresh MS
Nematzadeh D, see Kim YD
Neto GD, see Buckley FP
Neubauer KR, Kaufman RD. Another use for mass spectrometry: detection and monitoring of malignant hypothermia 837
Newberg LA. Use of intravenous glucose solutions in surgical patients 558
  see Laughlin TP
  see Messick JM
Newsome LR, Moldenhauer CC, Hug CC Jr, Nagle DM, Curling PE. Hemodynamic interactions of moderate doses of fentanyl with etomidate and ketamine (abstract) 260
Nguyen HD, see Nagashima H
Nicholas JF, see Manninen PH
Niemann K, see Ebert J
Nigrovic V, Auen M, Wajskol A. The role of the enzymatic hydrolysis of atracurium in vivo (abstract) 261
  Pandya JB, Auen M, Wajskol A. Inactivation of atracurium in human and rat plasma 1047
Nishimura K, see Yukioka H
Niswander D, see Goldberg M
Nordby EJ, see Moss J
Norman PF, see Bruce DL
Noueihid R, see Daily PA
Nugent M, see Messick JM
  see Roth JL
Okamoto K, Komatsu T, Bhalodia R, Kubal K, Shibutani K. Effects of the mechanical ventilation on thermodilution cardiac output measurements in man (abstract) 262
Oliver WC, see McMichan JC
Omote K, see Iwasaki H
Omote T, see Iwasaki H
Ono K, see Iwatsuki N
Opperman S, see Krajcirik WJ
Ording H. Incidence of malignant hyperthermia in Denmark 700
Osaki S, Gotoh Y, Nakaya H, Azuma M, Kanno M. Electrophysiologic effects of enflurane and halothane on isolated rabbit hearts in the presence and absence of metabolic acidosis 1060
Ostheimer GW, see Sinatra RS
Östman M, see Reiz S
O'Sullivan GM, Bullingham RE. Noninvasive assessment by radiotelemetry of antacid effect during labor 95
Oto M, see Roizen MF
Pace NL. Ever more statistics (editorial) 561
  see Bailey PL
  see Giese JL
  see Meline LJ
  see Stockham RJ
Packer DL, see Griffeth JK
Pai U, see Hartrick CT
Pairolero P, see McMichan JC
Palahniuk RJ, see Kozody R
Pandya JB, see Nigrovic V
Park WY, Kim SJ, Macnamara TE. Epidural anesthesia in patients with previous lumbar laminectomy or spinal fusion (abstract) 263
Parker KC, see Parker WD Jr
Parker WD Jr, Parker KC. Anesthesia-related transient aphonia and quadriplegia (letter) 1038
Pathak KS, Anton AH, Sutheimer CA. Effects of low-dose morphine and fentanyl infusions on urinary and plasma catecholamine concentrations during scoliosis surgery 509
Patrignani P, see Lichtenthal PR
Paulus DA, Basta JW, Klie H, Radson EA. Preanesthetic checklist (abstract) 264
Pearson J. Prolonged anesthesia with isoflurane (letter) 92
Person DL, Kissin I, Brown PT, Xavier AV, Vinik HR, Bradley EL. Morphine–caffeine analgesic interaction in rats 851
Peter J, see Drenger B
Peterson DO. Shoulder block anesthesia for shoulder reconstruction surgery 373
Petkau AJ, Coté CJ
Philip BK. Supplemental medication for ambulatory procedures under regional anesthesia 1117
  Philip JH. Avoiding air infusion with pressurized infusion systems: a new hazard (letter) 382
  see Sinatra RS
Philip JH, see Philip BK
Pinchak AC, Sung JC, Hagen JF, Hall F. Waiting time alters inhibition of succinylcholine fasciculations by atracurium (abstract) 265
Pither CE, see Hartrick CT
Plewes JL, Farhi LE. Cardiovascular and peripheral blood flow responses to prolonged controlled hypotension in the dog (abstract) 266
Plume SK, see Weinlander CM
Plummer JL, de la M Hall P, Jenner MA, Cousins MJ. Sex differences in halothane metabolism and hepatotoxicity in a rat model 563
Porges SW, see Donchin Y
Porter RW, see Reitan JA
Powell WF. A double-blind comparison of multiple intramuscular doses of ciramadol, morphine, and placebo for the treatment of postoperative pain 1101
Pratilas V, see Griffin RM
  see Wojtczak JA
Price C, see Price DD
Price DD, von der Gruen A, Miller J, Raffii A, Price C. Potentiation of systemic morphine analgesia in humans by proglumide, a cholecystokinin antagonist 801
Prichard JG, see Tidyman M
Prichep L, see Sommer RM
Primer G, see Moleski RJ
Proctor J, see Ebert J
Prough DS, see Balestrieri FJ
Prutow RJ, see Drummond JC
Quinn ML, see Bolsin SN
Quintin L. Pressurized infusion system (letter) 458
Radel TJ, Fallacaro MD, Sievenpiper TS, Whalen DA Jr. Intraoperative evaluation of a warming vest and cap during lower extremity orthopedic procedures (abstract) 267
Radson EA, see Paulus DA
Raffii A, see Price DD
Raj P, see Hartrick CT
Ramanathan J, Bottorff M, Sibai BM. Maternal and neonatal effects of epidural lidocaine in preeclamptic women undergoing cesarean section (abstract) 268
Ramanathan S, see Feldstein G
  see Rock I
  see Sheth R
Ramasubramanian R, see Verma R
Ramseur A, see Greene SJ
Rao CC, see Means LJ
Rao TLK, see Healy P
  see Jacobs HK
Rapp J, see Roizen MF
Raval RR, Fan FC, Samojlik E. Etomidate and adrenocortical suppression (abstract) 269
Rawal N, Schott U, Tandon B, Sjöstrand U, Wennhager M. Influence of I.V. naloxone infusion on analgesia and untoward effects of epidural morphine (abstract) 270
Raya JA, see Daily PA
Rayburn RL. Gas flows with a coaxial circuit at 1.3 and 2.3 MAC halothane in spontaneously breathing children (abstract) 271
Raymond SA, see Rocco AG
Rector FTR, DeNuccio DJ, Alden MA, Kimball RS. Atomizer modification for nasal administration of cocaine and other drugs 739
Redpath JH, see Ham J
Reeves JL, see Eich E
Refsum H, see Hotvedt R
Rehkopf P, see Rubiano R
Rehnberg KA, see Lichtenthal PR
Reitan JA, Porter RW, Braunstein M. Comparison of psychomotor skills and amnesia after induction of anesthesia by midazolam or thiopental (abstract) 272

Reiz S, Östman M. Regional coronary hemodynamics during isoflurane–nitrous oxide anesthesia in patients with ischemic heart disease 570
Rempel WE, see Gallant EM
Reves JG, deBruijn N, Kates RA. Sensitive measures of outcome (letter) 751; with response by Roizen MF
  see Adams P
  see Menkhaus PG
Reynolds WJ, see Baumgarten RK
Rhodes RS, see Lina AA
Richards D, see Royster RL
Rimback G, see Cassuto J
Ripp CH, Chapin JW. A bellow's leak in an Ohio anesthesia ventilator (letter) 942
Ritchie PA, see Tierney E
Roberts CP, see Dagnino J
Rocco AG, Raymond SA, Murray E, Dhingra U, Freiberger D. Differential spread of blockade of touch, cold, and pinprick during spinal anesthesia 917
Rock I, Sheth R, Ramanathan S, Arismendy J, Turndorf H. Glucose metabolism in the mother and fetus during cesarean section under epidural anesthesia (abstract) 273
Rodgers GM, see Roizen MF
Rogers K, see Chelly J
Rogers MC, see Wetzel RC
Rogers SN, Benumof JL. Halothane and isoflurane do not decrease $PaO_2$ during one-lung ventilation in intravenously anesthetized patients 946
Roizen MF, Dandekar PV, Cahalan MK, Cronnelly R, Dailey PA, Litt L, Eger EI II, Rosen MA, Sohn YJ, Glass RH, MacKenzie NL. Effect of nitrous oxide on in vitro fertilization success rate (abstract) 274
  Lampe GH, Sheiner LB, Alpert RA, Frazer BM, Chan RP, Eger EI II. Aging increases hemodynamic responses to induction and incision (abstract) 275
  Rodgers GM, Valone FH, Lampe GH, Benefiel DJ, Smith JS, Cherry KP, Rapp J, Oto M, Goetzl EJ. Anaphylactoid reactions to vascular graft material (abstract) 276
  see Moss J
  see Reves JG
Ronai AK, see Avram MJ
  see Berry AJ
  see Greene SJ
  see Sloan T
Rose JC, see Kim YD
Rosen MA, Thigpen JW, Shnider SM, Foutz SE, Levinson G, Koike M. Bupivacaine-induced cardiotoxicity in hypoxic and acidotic sheep 1089
  see Eisler EA
  see Roizen MF
Rosenberg PH, Heaver JE. In vitro study of the effect of epidural blood patch on leakage through a dural puncture 501
Ross WT Jr, see Stirt JA
Rossi EC, see Lichtenthal PR
Roth JL, Nugent M, Gronert GA. Verapamil does not alter succinylcholine-induced increases in serum potassium during halothane anesthesia in normal dogs 1202
Rothstein P, see Tanner GE
Roule M, see Borland LM
Roush JR, see Manchikanti L
Roy L, see Blaise G
Roy WL, see Collins C
Royster RL, Johnston WE, Gravlee GP, Brauer S, Richards D. Arrhythmias during venous cannulation prior to pulmonary artery catheter insertion 1214
Rubiano R, Chang J-L, Larson CE, Lawler RA, Rehkopf P. Precautions in use of a new endotracheal tube for laser surgery (letter) 1037
Rudd GD, see Brandom BW
Russel IF. Balanced anesthesia: does it anesthetize? (letter) 941
Rusy BF, see Ewart RBL
  see Komai H
Sachar RM, see Verma R
Saddler JM, James MFM, Cork RC. Ethanol reversal with naloxone (abstract) 277
Saito Y, see Yamamura T
Saklad J, see Toung TJK
Salem R, see Jacobs HK
Samojlik E, see Raval RR
Samonte AF, see Starr NJ
Samra SK, Kroll DA. Subarachnoid hemorrhage and intraoperative electrocardiographic changes simulating myocardial ischemia—anesthesiologist's dilemma 86
  see Hill AB
Samuelson PN, see Menkhaus PG
Sanford TJ Jr, see Bolsin SN
Saumet J-L, see Degoute C-S
Savarese JJ, Ali H, Basta SJ, Sunder N, Scott RFP, Gargarian M, Gionfriddo M, Weakly JN, Batson AG. Neuromuscular and cardiovascular effects of BW B1090U in anesthetized volunteers (abstract) 278
  see Ali H
  see de Bros FM
Schatz GC, see Berry AJ
Schauble JF, see Backofen JE
Scheller MS, see Drummond JC
Scherpereel P, see Chrubasik J
Schiebel F, see Teba L
Schmitt BI, see Lerman J
Schott U, see Rawal N
Schreiner E. An unusual complication of the arrow radial artery kit (letter) 844
Schrier RI, see Moleski RJ
Sclabassi RJ, see Ingram MD
Scott RFP, see Ali H
  see de Bros FM
  see Savarese JJ
Sear J, Moore A, Hunniset A, Baldwin D, Allen M, Hand C, McQuay H, Morris P. Morphine kinetics and kidney transplantation: morphine removal is influenced by renal ischemia 1065
Sebel PS, see Waldmann CS
Senami M, Aoki M, Kitahata LM, Yuge O, Collins JG. Does morphine analgesia produce changes in peripheral nerve function in cats? 279
  see Aoki M
  see Yuge O
Sethna DH, see Starr NJ
Setzer N, see Wetzel RC
Shahangian S, see Wang JM
Shanks CA, see Avram MJ
  see Greene SJ
Shapira Y, see Drexler H
Shapiro DA, see Eisler EA
Shaw BW, see Kang YG
Shayevitz JR, Matteo RS. Decreased sensitivity to metocurine in patients with upper motoneuron disease 767
Sheikh-Ol-Eslam A, see Abboud TK
Sheiner LB, see Roizen MF
Sheth AP, Dautenhahn DL, Fagraeus L. Decreased CSF protein during pregnancy as a mechanism facilitating the spread of spinal anesthesia (abstract) 280
Sheth R, Ramanathan S, Durtzman M, Turndorf H. Obstetrical anesthesia for patients with genital herpes: a retrospective study (abstract) 281
  see Rock I
Shi W-Z, Fahey MR, Fisher DM, Eger EI, Canfell C, Miller RD. Increase in minimum alveolar concentration (MAC) of halothane by laudanosine in rabbits (abstract) 282
Shibutani K, see Okamoto K
Shier NQ, see Moleski RJ
Shigematsu T, Wang H, Nagano M. Trigeminal nerve palsy after lumbar epidural anesthesia (letter) 653
Shilyanski G, see Murad SHN
Shnider SM, see Daily PA
  see Eisler EA
  see Rosen MA
Shulman D, see Beilin B
Sibai AN, see Baraka A
Sibai BM, see Ramanathan J
Sievenpiper TS, see Radel TJ

Siker ES. Quality of care in anesthetic practice (book review) 464
Silvay G, Mindich BP, Burgess NL, Girard D, Thys DM, Kaplan JA. Coronary artery bypass graft surgery without cardiopulmonary bypass (abstract) 283
Sinatra RS, Philip BK, Naulty JS, Ostheimer GW. Prolonged neuromuscular blockade with vecuronium in a patient treated with magnesium sulfate 1220
Sipes IG, see Lind RC
Sivarajan M, Amory DW, McKenzie SM. Regional blood flows during induced hypotension produced by nitroprusside or trimethaphan in the rhesus monkey 759
Sjöstrand U, see Rawal N
Skinner D, see Tremper KK
Skourtis CT, Athanasiadis C, Ali H, Lappas DG, Mihelakos P. Neuromuscular and circulatory responses to atracurium during administration of high dose of fentanyl (abstract) 284
  see Athanasiadis C
Sladen RN. Temperature and ventilation after hypothermic cardiopulmonary bypass 816
Slaymaker F, see Fraulini KE
Sloan T, Koht A, Ronai A, Toleikis JR. Events associated with intraoperative evoked potential changes correlation with postoperative neurological status (abstract) 285
Smith B, see Goudsouzian NG
  see Jacobs HK
Smith C, see Gaba D
  see Hayward E
  see Spiss CK
Smith JS, see Roizen MF
Smith LE, see Barber WB
Smith M, see Abraham E
Smith NT, see Bolsin SN
Smith RB III, see Weitz FI
Smuckler EA, see Fassoulaki A
  see Fisher NA
Snider MT, see Morita S
Sohn YJ, see Roizen MF
Sommer RM, Prichep L, Malarik P, Turndorf H. Effect of thiopental on brainstorm auditory evoked responses (abstract) 286
Sosis M. Violent fasciculations may not signal pseudocholinesterase deficiency (letter) 557; with response by Glasser SA
  Amoroso M. Respiratory insufficiency after gastrostomy prior to tracheoesophageal fistula repair 748
Spielman FJ, see Dewan DM
Spiss CK, Smith CM, Tsujimoto G, Hoffman BB, Maze M. Prolonged hyporesponsiveness of vascular smooth muscle contraction after halothane anesthesia in rabbits 1
  see Berry AJ
  see Hayward E
Spivey DL. Epinephrine does not prolong lidocaine spinal anesthesia in term parturients 468
Sprague DH, see Lineberger AS III
Stanley TH, see Bailey PL
  see Giese JL
  see Stockham RJ
Starr NJ, Sethna DH, Samonte AF, Estafanous FG. Hemodynamic comparison of non-depolarizing muscle relaxants: a randomized prospective study (abstract) 287
Starzl TE, see Kang YG
Steen SN, see Joseph MM
Stein C, see Liwak B
Sternick CS, see Stirt JA
Stevenson RL, Beattie C, Jacobson RC. Arrhythmias and conduction disturbances related to Swan-Ganz catheterization (abstract) 288
Stiers WM, see Avram MJ
Stiff JL, see Wetzel RC
Stiller RL, Brandom BW, Cook DR. Determination of atracurium in plasma by high-performance liquid chromatography 58
  Cook DR, Chakravorti S. In vitro degradation of atracurium in human plasma (abstract) 289
  see Ingram MD
Stirt JA, Brown RE Jr, Ross WT Jr, Althaus JS. Atracurium in a patient with pheochromocytoma 547
  Stone DJ, Weinberg G, Willson DF, Sternick CS, Sussman MD. Atracurium in a child with myotonic dystrophy 369
  see Finholt DA
  see Minton MD
  see Nakatsu K
  see Weinberg G
Stockham RJ, Stanley TH, Groen F, Gillmor ST, Pace NL, King K. Fentanyl vs etomidate plus fentanyl for anesthetic induction in high risk patients (abstract) 290
  see Giese JL
Stoelting RK, see Karasek J
Stone DJ, see Stirt JA
Stullken EH, see Balestrieri FJ
Sullivan SF, see Nakatsu K
Sunder N, see Ali H
  see Savarese JJ
Sung JC, see Pinchak AC
Sung M-L, see White PF
Suresh MS, Nelson TE. Malignant hyperthermia: is etomidate safe? 420
Sussman MD, see Stirt JA
Sutheimer CA, see Pathak KS
Suzukawa M, see Yuge O
Swartz J, see Kozody R
Swen J, Gencarelli PJ, Koot HWJ. Vecuronium infusion dose requirements during fentanyl and halothane anesthesia in humans 411
Szyfelbein SK, see Martyn JAJ
Tabatabai M. Post-anesthetic recovery (book review) 94
  see Yuge O
Tabsh KMA, see Murad SHN
Takahashi T, see Iwasaki H
Tamura M, Kawano T, Fitz-James I, Bryan AC. High-frequency oscillatory ventilation and pulmonary extra-vascular water 1041
Tanaka A, see Yuge O
Tandon B, see Rawal N
Tanner GE, Angers DG, Barash PG, Mulla A, Miller PL, Rothstein P. Effect of left-to-right, mixed right-to-left, and right-to-left shunts on inhalational anesthetic induction in children: a computer model 101
Tantisira B, see Tyler IL
Tapia DP, see Dadabhoy ZP
Tasch MD. Myoclonus on recovery from etomidate (letter) 943
Taylor A, see Chelly J
Teba L, Zakaria M, Schiebel F. Guide wire complication during central vein catheterization (letter) 460
Templeton JJ, see Lee KWT
Theiss D, see Lanz E
  see Murphy DF
Thiagarajah S, Azar I, Lear E. The effect of diltiazem on intracranial pressure in cats (abstract) 291
  see Azar I
Thigpen JW, see Daily PA
  see Rosen MA
Thisted R, see Moss J
Thistlewood JM, see Dewan DM
Thompson GE. Current concepts in regional anaesthesia (book review) 464
  Plexus anesthesia, volume I, perivascular techniques of brachial plexus block (book review) 654
Thompson J, see Berry AJ
Thys D, Cohen E, Eisenkraft JB, Kaplan JA. The pulse oximeter, a non-invasive monitor of oxygenation during one-lung anesthesia (abstract) 292
  Hillel Z, Mindich B, Goldman M, Kaplan JA. Effects of sodium nitroprusside on systemic hemodynamics following cardiopulmonary bypass for CABG (abstract) 293
  see Cohen E
  see Girard D
  see Hillel Z
  see Silvay G

Tidyman M, Prichard JG, Deamer RL, Mac N. Adjunctive use of dantrolene in severe tetanus 538
Tierney E, Ritchie PA, Hain WR, Cooke RA. Halothane or enflurane for inhalation induction? A study of children's preferences 77
Tippit SE, see Kapur PA
Todd MM, Drummond JC, U HS. The hemodynamic consequences of high-dose thiopental anesthesia 681
Toleikis JR, see Sloan T
Tomsick TA, see Hartrick CT
Toung TJK, Grayson R, Saklad J, Wang H. Movement of the distal end of the endotracheal tube during flexion and extension of the neck (letter) 1030
Tremper KK, Hufstedler SM, Zaccari J, Lee V, Skinner D, Weiss M, Cross B. Transcutaneous and liver surface $Po_2$ during normotensive shock in dogs (abstract) 294
  see Lin SK
Triner L, see Bernstein KJ
Trouwborst A, Erdmann W, Yanagida H, Corssen G. Electrophysiologic evidence for involvement of the pituitary region in opiate analgesia 781
Trudell JR. Equilibrium of 1% halothane with components of the central nervous system (letter) 847
  Is there light at the end of the tunnel? 385
Tsang M, see Abraham E
Tsujimoto G, see Spiss CK
Turnbull C, see Levy JH
Turndorf H, see Rock I
  see Sheth R
  see Sommer RM
  see Wang BC
Tverskoy M, Gelman S, Fowler KC, Bradley EL. Influence of fentanyl and morphine on intestinal circulation 577
Tyler IL, Tantisira B, Winter PM, Motoyama EK. Continuous monitoring of arterial oxygen saturation with pulse oximetry during transfer to the recovery room 1108
U HS, see Todd MM
Ueda I, see Gillman MA
Umeda S, Arai T. Disulfiram-like reaction to moxalactam after celiac plexus alcohol block (letter) 377
Unadkat JD, see Carpenter RL
Valanne J, see Korttila K
Valone FH, see Roizen MF
Vandam LD. A calculus of suffering. Pain, professionalism, and anesthesia in nineteenth century America (book review) 1229
van der Starre PJA, Harinck-de Weerd J. Comparative study between nitroprusside and ketanserin in the treatment of hypertension following coronary artery bypass grafting (abstract) 304
van der Zee HT, Faithfull S, Kuypers MH, Dhasmana KM, Erdmann W. On-line conjunctival oxygen tension as a guide to cerebral oxygenation 63
Van Etten AP, see Flacke JW
Van Gorder PN, Hoffman WE, Baughman V, Albrecht RF, Miletich DJ, Guzman F, Cook JM. Midazolam—ethanol interactions and reversal with a benzodiazepine antagonist 129
Varner PD, Ebert JP, McKay RD, Nail CS, Whitlock TM. Methohexital sedation of children undergoing CT scan 643
Vatashsky E, see Beilin B
Verma R, Ramasubramanian R, Sachar RM. Anesthesia for termination of pregnancy: midazolam compared with methohexital 792
Verosky M, see Bernstein KJ
Villalonga A, Beltran J, Gomar C, Nalda MA. Ketamine for treatment of priapism (letter) 1033
Vinik HR, see Person DL
Vinograd I, see Beilin B
von der Gruen A, see Price DD
Wade JG, see Kozody R
Wade LD, see Kinzer JB
  see Lichtenthal PR
Wagner R, see Bazaral MG
Wajskol A, see Nigrovic V
Waldmann CS, Wark KJ, Sebel PS, Feneck RO. Hemodynamic effects of atracurium, vecuronium and pancuronium during sufentanil anesthesia during elective coronary artery surgery (abstract) 295
Wallin G, see Cassuto J
Wang BC, Hillman DE, Turndorf H. The effect of pH on subarachnoid blockade with sodium metabisulfite in rabbit (abstract) 296
Wang H, see Shigematsu T
  see Toung TJK
Wang JM, Wong KC, Creel DJ, Clark WM, Shahangian S. Effects of glycine on hemodynamic responses and visual evoked potentials in the dog 1071
Wangler MA, Kilpatrick DS. Aminophylline is an antagonist of lorazepam 834
Wark KJ, see Waldmann CS
Warneck CM, see Flacke JW
Warner DL, see Joseph MM
Watkins ML, see Buzello W
Waud BE, Amaki Y, Waud DR. Disuse and *d*-tubocurarine sensitivity in isolated muscles 1178
  see Amaki Y
Waud DR, see Amaki Y
  see Waud BE
Wauquier A, see Ashton D
Weakly JN, see Savarese JJ
Weinberg G, Stirt JA, Longnecker DE. Single versus divided doses of atracurium: does 0.05 + 0.10 equal 0.15? (abstract) 298
Weinberg G, see Stirt JA
Weinlander CM, Coombs DW, Plume SK. Myocardial ischemia due to obstruction of an aortocoronary bypass graft by intraoperative positioning 933
Weintraub SJ, Naulty JS. Acute abstinence syndrome after epidural injection of butorphanol 451
Weiss JL, see Cork RC
Weiss M, see Tremper KK
Weitz FI, Berry AJ, Smith RB III, Levy JH. Noninvasive detection of ischemic ventricular dysfunction by cardiokymography in patients undergoing abdominal aortic surgery (abstract) 297
Weldon ST, Williams-Van Alstyne SI, Gandolfi AJ, Blitt CD. Production and characterization of impurities in isoflurane vaporizers 634
Wennhager M, see Rawal N
Wessel DL, see Hickey PR
Westenskow DR, see Meline LJ
Westover CJ Jr, see Bolsin SN
Wetzel RC, Setzer N, Stiff JL, Rogers MC. Hemodynamic responses in brain dead organ donor patients 125
Whalen DA Jr, see Radel TJ
White PF, Sung M-L. Use of opiate infusions in anesthesia-determining optimal doses and serum concentrations (abstract) 299
Whitlock TM, see Varner PD
Wijetilleka SA, see Hirsch NP
Wilbrink J, see Bailey PL
Williams CH, Buzello W, Dozier SE, Chandra P, Gehrke CW, Gerhardt KO, Wong JK. Hemodynamics, cardiac function, oxygen use and catecholamines during porcine malignant hyperthermia 300
  Dozier SE, Ilias WK, Fulfer RT. Porcine malignant hyperthermia: testing of atracurium in MH susceptible pigs (abstract) 301
  see Buzello W
Williams-Van Alstyne SI, see Weldon ST
Willis MM, see Lerman J
Willson DF, see Stirt JA
Win KK, see Joseph MM
Winnie AP, see Korenaga GM
Winter PM, see Kang YG
  see Tyler IL
Wisborg T, see Leicht P

Woelfel SK, see Brandom BW
Wojtczak JA, Griffin RM, Pratilas V, Kaplan JA. Mechanisms of arrhythmias during bupivacaine intoxication in rabbits—in vitro and in vivo study (abstract) 302
  Kaplan JA. Effects of general and local anesthetics on intercellular electrical coupling in heart muscle (abstract) 303
Wolf PH, see Kim YD
Wong AB, see Gravlee GP
Wong DH, see Flacke JW
Wong JK, see Williams CH
Wong KC, see Wang JM
Wood AJJ, see Gordon L
Wood M, see Gordon L
Wright BD, see Hinkley RE Jr
Wünsch E, see Chrubasik J
Xavier AV, see Person DL
Yamamura T, Furumido H, Saito Y. A single-unit device for differential lung ventilation with only one anesthesia machine 1017
Yamut F, see Baraka A
Yanagi T, see Abboud TK
Yanagida H, see Trouwborst A
Yoshimoto N, see Yukioka H
Yuge O, Kitahata LM, Collins JG, Matsumoto M, Tabatabai M, Suzukawa M, Tanaka A. Fentanyl and alfentanil suppress brainstem pain transmission 597
  Matsumoto M, Kitahata LM, Collins JG, Senami M. Direct opioid application to peripheral nerves does not alter compound action potentials 667
  see Senami M
Yukioka H, Yoshimoto N, Nishimura K, Fujimori M. Intravenous lidocaine as a suppressant of coughing during tracheal intubation 1189
Zaccari J, see Tremper KK
Zakarian M, see Abboud TK
  see Teba L
Zaloga GP, see Barber WB
Zaroura S, see Drexler H
Zhen-Lin R, see Ming-de W
Zinn SE, Fairley HB, Glenn JD. Liver function in patients with mild alcoholic hepatitis, after enflurane, nitrous oxide—narcotic, and spinal anesthesia 487
Zsigmond EK, see Dadabhoy ZP
  see Korenaga GM
Zwanikken P, see Bailey PL

ANESTH ANALG
1985;64:1249–57

# Subject Index

- **Abortion,** see Pregnancy
- **Acetylcholine**
  - brain, halothane effects on 385, 395
- **Acid–base equilibrium**
  - pH sensor of, intravascular 731
- **Adenosine monophosphate,** see Metabolism
- **Adenylate cyclase,** see Enzymes
- **Age factors**
  - (abstract) 275
  - in pulmonary aspiration risk factor assessment 11
  - in volatile anesthetic solubility 640, 1097
- **Airway**
  - obstruction, croup and epiglottitis-induced 621
- **Alcohol**
  - celiac plexus block with (letter) 377
  - ethanol
    - midazolam–ethanol interactions 129
    - naloxone reversal of (abstract) 277
- **Alfentanil,** see Analgesics
- **Allergy**
  - chymopapain
    - incidence and mortality of 1197
    - (letter) 90
  - pancuronium (letter) 944
  - vascular graft material (abstract) 276
- **Ambulatory,** see Anesthesia, outpatient
- **Aminophylline,** see Pharmacology
- **Analeptics**
  - caffeine, morphine interaction with 851
- **Analgesics**
  - addiction, withdrawal syndrome with 451
  - alfentanil
    - in brainstem pain transmission suppression 597
    - potency and effectiveness of, compared to morphine 807
  - with biliary tract disease (letter) 379
  - buprenorphine, epidural, for postoperative pain (letter) 456
  - butorphanol, acute abstinence syndrome and 451
  - ciramadol, morphine comparison to 1101
  - control systems for 989
  - fentanyl
    - autonomic tone deprivation and effects of 1053
    - brainstem pain transmission suppression with 597
    - cirrhotic liver function affected by 1183
    - comparative study of 897
    - hemodynamic responses to, in infants 483
    - intestinal circulatory effects of 577
    - patent ductus arteriosus ligation in preterm infants with 1078
    - peripheral nerve action potentials with 667
    - pituitary gland in mechanism of action of 781
    - stress responses in pulmonary circulation affected by 1137
  - meperidine
    - comparative study of 897
    - neonatal behavior affected by low doses of 335
  - morphine
    - (abstract) 211, 214, 258, 279
    - brain and spinal cord concentration after subarachnoid injection 929
    - caffeine interactions with 851
    - ciramadol comparison to 1101
    - comparative study of 897
    - dose–response study for epidural administration 786
    - intestinal circulatory effects of 577
    - kinetics of, in kidney transplantation 1065
    - naloxone effects with intrathecal use of, in labor 658
    - peripheral nerve action potentials with 667
    - proglumide potentiation of 801
  - nalbuphine (abstract) 205, 258
  - opioids
    - comparative study of 897
    - mechanisms of (letter) 752
    - peripheral nerve action potentials with 667
    - pituitary gland in action of 781
    - proglumide potentiation of 801
- **Anaphylaxis,** see Allergy
- **Anesthesia**
  - cardiovascular
    - (abstract) 215
    - $\beta$-adrenceptor blockade assessment during 305
    - $\beta$-endorphin immunoreactivity with, plasma 677
    - blood pressure monitoring 1134
    - circulatory shunts affecting inhalation induction 101
    - fentanyl
      - coronary artery disease and usage of 312
      - stress response in pulmonary circulation with 1137
      - sufentanil vs 877
    - hypoxemia from leaks in gas supply system (letter) 649
    - pulmonary artery catheterization in (letter) 844
    - temperature and ventilation after 816
    - vent stitch entrapment in (letter) 379
    - verapamil, for nitroglycerin-refractory myocardial ischemia 68
  - dental, sublingual emphysema complicating 737
  - electroshock, MAO inhibitor discontinuation prior to 592
  - geriatric, metocurine and tubocurarine in 23
  - neurosurgical
    - ECG changes simulating myocardial ischemia and 86
    - intracranial pressure after atracurium 1113
    - for nonneurosurgical patient with CNS pathophysiology 143
    - priorities in (letter) 942
    - subarachnoid hemorrhage and 86
    - thiopental hemodynamic effects in high doses 681
  - obstetric
    - aortocaval compression with inflation device 1015
    - bupivacaine lumbar epidural analgesia with epinephrine 585
    - 2-chloroprocaine effects on neonatal behavior (letter) 1223
    - citrate pretreatment for cesarean section 34
    - comparison of anesthetic agents for cesarean section (abstract) 233
    - general vs regional anesthesia for cesarean section 996
    - genital herpes and (abstract) 281
    - glucose metabolism during cesarean section (abstract) 273
    - lidocaine for cesarean section, epidural (abstract) 268
    - magnesium pretreatment for cesarean section (abstract) 202
    - magnesium sulfate interaction with vecuronium 1220
    - meperidine effects on neonatal behavior 335
    - morphine usage in labor, intrathecal with naloxone 658
    - radiotelemetric assessment of antacid effect during labor 95
    - spinal anesthesia spread, decreased CSF protein in (abstract) 280
    - termination of pregnancy 792
    - verapamil effects on uterine blood flow and maternal cardiovascular function 7
  - otolaryngologic, lidocaine for laryngospasm prevention in 1193
  - outpatient
    - (abstract) 239
    - supplemental medication for 1117
  - pediatric
    - atracurium
      - infusion requirements 471
      - myotonic dystrophy and 369

**Anesthesia**—*continued*
- pediatric—*continued*
  - with circulatory shunts 101
  - croup and epiglottitis with airway obstruction 621
  - fentanyl
    - patent ductus arteriosus ligation with 1078
    - pulmonary and hemodynamic responses to 483, 1137
  - halothane vs enflurane inhalation induction 77
  - orthotopic liver transplantation 117
- thoracic
  - differential lung ventilation in, device for 1017
  - hypoxic pulmonary vasoconstriction in 821, 946
  - one-lung ventilation in 821, 946
    - (letter) 1036

**Anesthesiologists**
- hepatitis B risk among 672
- occupational hazards (letter) 93

**Anesthesiology**
- textbooks, subjective evaluation of 362

**Anesthetic techniques**
- balanced (letter) 941
- closed circuit
  - altitude effects on (letter) 843
  - nonanesthetic gas contamination of 343
  - trace gaseous metabolites in (letter) 1029
- counter-irritation, during cutaneous needle insertion (letter) 379
- endobronchial, with one-lung ventilation 821
  - (letter) 1036
- epidural
  - (abstract) 262
  - aphonia and quadriplegia with 365
    - (letter) 1038
  - blood patch
    - dural puncture leakage and 501
    - outpatient procedures (letter) 458
  - bupivacaine, lumbar, with epinephrine 585
  - buprenorphine for postoperative pain
    - (letter) 456
  - extracorporeal shock wave lithotripsy 544
  - ketamine, for postoperative pain 1161
  - morphine, double-blind study of dosages for 786
  - paraplegia as complication of 937
  - previous spinal surgery and 83
  - somatostatin for postoperative pain 1085
  - spinal fusion and (letter) 843
  - subdural migration of catheter in 175
    - (letter) 1029
  - transcatheter serial phenol neurolysis 1205
  - trigeminal nerve palsy from (letter) 653
- hypotensive
  - (abstract) 304
  - cardiovascular and peripheral blood flow response to 260
  - neuroendocrine and hemodynamic responses to 208
  - nitroglycerin-induced vasodilation 30
  - nitroprusside
    - (abstract) 229, 293, 304
    - computer-controlled infusion 38
    - regional blood flow during 759
  - trimethaphan effects 759
- one-lung ventilation 821, 946, 1017
  - (letter) 1036
- regional
  - brachial plexus (letter) 646
  - infiltration, hemodynamic and plasma catecholamine responses to 924
  - nerve stimulator in 1217
  - shoulder block, for shoulder reconstruction surgery 373
  - sympathetic blockade, complete 415
  - touch, cold, and pinprick blockade, differential spread of 917
- spinal
  - (abstract) 196, 280, 296
  - distribution of solution within subarachnoid space 715
  - failure of, incidence and causes of 705
  - morphine concentration in brain and spinal cord after subarachnoid injection 929

**Anesthetics, gases**
- nitrous oxide
  - (abstract) 274
  - brainstem auditory evoked potentials with 43
  - halothane-induced hepatic injury and 465
  - mechanisms of (letter) 752
- trace concentrations
  - (letter) 90, 377
  - teratogenicity of 981

**Anesthetics, intravenous**
- control systems for 989
- droperidol (abstract) 227
- etomidate
  - (abstract) 269
  - GABA-ergic inhibitory circuit in hippocampus modulated by 975
  - malignant hyperthermia and 420
  - myoclonus from 80
    - (letter) 943, 1034
  - negative inotropic effect in papillary muscle 400
  - seizures from (letter) 1226
  - thiopental vs, for induction 871
- fentanyl
  - (abstract) 254, 255, 260
  - catecholamine concentrations affected by, during surgery 509
  - coronary artery disease and 312
  - $\beta$-endorphin immunoreactivity with 677
  - familial dysautonomia and 72
  - fertilization and early development of sea urchin eggs with 498
  - induction effects 48
    - (abstract) 290
  - patent ductus arteriosus ligation with 1078
  - sufentanil vs, for cardiac anesthesia 877
  - vecuronium infusion dose requirements during 411
- ketamine
  - postoperative pain therapy with epidural 1161
- lidocaine
  - arrhythmia treatment with 911
  - coughing suppression with, during intubation 1189
  - hemodynamic and plasma catecholamine responses to 924
  - intraocular pressure affected by 1211
  - laryngospasm prevention with, after extubation 1189
  - postoperative pain inhibition by 971
- methohexital
  - hemodynamic consequences of high dosages of 681
  - pregnancy termination with 792
- morphine
  - catecholamine concentrations affected by, during surgery 509
- narcotics
  - (abstract) 299
  - comparative study 897
- opioids
  - urinary and plasma catecholamines during surgery with 509
- sufentanil
  - (abstract) 190, 295
  - analgetic effect during halothane anesthesia 857
  - fentanyl vs, for cardiac anesthesia 877
- thiopental
  - (abstract) 286
  - aminophylline antagonism of residual effects of (letter) 1034
  - etomidate vs, for induction 871
  - hemodynamic consequences of high dosages of 681
  - requirements for children after recovery from thermal injury 1156

**Anesthetics, local**
- bupivacaine
  - (abstract) 209, 302
  - cardiovascular toxicity of 911, 1089
  - convulsions and ventricular tachycardia from (letter) 844
  - electrophysiologic and hemodynamic effects on heart 388
  - obstetric analgesia with 585
  - overdosage of, cardiovascular resuscitation after 491
  - pH effects on 477
- 2-chloroprocaine effects on neonatal behavior (letter) 1223

- cocaine
  - atomizer modification for nasal administration of 739
  - substitutes for 457
- distribution of, within subarachnoid space 715
- lidocaine
  - (abstract) 268
  - as cocaine substitute 457
  - pH effects on 477
  - spinal anesthesia with, epinephrine effect on 468
- pH effects 477
- toxicity 1089
  - (abstract) 204
  - (letter) 559

**Anesthetics, volatile**
- (abstract) 220, 221
- enflurane
  - (abstract) 231
  - cirrhotic liver function affected by 1183
  - electrophysiologic effects of, on heart 1060
  - hepatotoxicity of 955
  - hormonal and hemodynamic responses to, with hypertension 136
  - inhalation induction with 77
  - insulin secretion rates affected by 18
  - partition coefficients of, in fluosol 405
  - solubility of
    - age factors 640, 1097
    - temperature factors 640
  - teratogenicity from, incidence of 1005
- halothane
  - (abstract) 219, 241
  - choline uptake, acetylcholine synthesis and release with 385, 395
  - cirrhotic liver function affected by 1183
  - diltiazem antiarrhythmic effect with 964
  - electrophysiologic effects of, on heart 1060
  - $\beta$-endorphin immunoreactivity with 677
  - equilibrium of, with components of central nervous system (letter) 847
  - hepatic adenylate cyclase effects of 531
  - hepatotoxicity of 955
    - (abstract) 250
    - repair of 465
    - sex differences in 563
  - hormonal and hemodynamic responses to, with hypertension 136
  - inhalation induction with 77
  - isoflurane inhibitory effect on 1171
  - morphine–alfentil comparison via MAC reduction of 807
  - one-lung ventilation with 946
  - partition coefficients of, in fluosol 405
  - sex differences in metabolism of 563
  - solubility of
    - age factors 640, 1097
    - temperature factors 640
  - subendothelial oxygen supply–demand balance and 1149
  - sufentanil analgetic contribution during 857
  - teratogenicity of, incidence of 1005
  - vascular smooth muscle contraction after, 1
  - vecuronium infusion dose requirements during 411
- isoflurane
  - (abstract) 234, 251
  - brainstem auditory evoked potentials with 43
  - cirrhotic liver function affected by 1183
  - coronary hemodynamics of, with cardiac ischemia 570
  - halothane-induced hepatic injury and 465
  - hepatic necrosis and dysfunction associated with 1131
    - (letter) 458
  - impurities in, production and characterization of 634
  - one-lung ventilation with 946
  - oxidative halothane metabolism inhibited by 1171
  - partition coefficients of, in fluosol 405
  - replantation surgery with (letter) 90
  - respiratory sinus arrhythmia during recovery from 811
  - seizure activity with 367
    - (letter) 1225
  - solubility of
    - age factors 640, 1097
    - temperature factors 640
- metabolites of (letter) 1029
- methoxyflurane
  - solubility of
    - age factors 640, 1097
    - temperature factors 640
  - teratogenicity of, incidence of 1005
- trace concentrations (letter) 378

**Angiotensin,** see Polypeptides

**Antacids,** see Gastrointestinal tract

**Antagonists, miscellaneous**
- proglumide, potentiation of morphine analgesia with 801

**Antagonists, narcotic**
- naloxone
  - (abstract) 270
  - with intrathecal use of morphine in labor 658

**Antagonists, neuromuscular relaxants**
- edrophonium, for atracurium neuromuscular block 867
- neostigmine
  - for atracurium neuromuscular block 867
  - for succinylcholine neuromuscular block 773

**Arrhythmias,** see Heart

**Aspiration,** see
- Complications
- Gastrointestinal tract, antacids
- Lung

**Asthma,** see
- Complications
- Lung

**Ataractics**
- monoamine oxidase inhibitors, preoperative discontinuance of, with ECT or elective surgery 592

**Atracurium,** see Neuromuscular relaxants

**Barbiturates,** see Hypnotics

**Benzodiazepines,** see Hypnotics

**Beta-adrenergic receptor,** see Sympathetic nervous system

**Bilary tract,** see Liver

**Biology**
- fertilization, fentanyl effects on sea urchin eggs 498

**Biotransformation (drug)**
- carboxylesterase 1047
- enzymatic hydrolysis 1047
- halothane
  - inhibitory effect of isoflurane 1171
  - sex differences 563
- Hofmann elimination 1047

**Blood**
- coagulation
  - heparin in 1081
  - intraoperative changes during liver transplantation 888
  - nitroglycerin dose-related effect on, intravenous 30
  - protamine in 348, 1081
    - (abstract) 230
    - (letter) 1033
- fluorocarbons, fluosol-DA
  - (abstract) 199
  - partition coeffients of enflurane, halothane, and isoflurane in 405
- plasma, fresh frozen 849

**Blood pressure**
- hypertension
  - hormonal/hemodynamic responses to halothane and enflurane with 136
- hypotension
  - diltiazem-induced, 1001
  - heparin- and protamine-induced 1081
  - nitroprusside-induced, computer-controlled regulation of 38
  - trimethaphan-induced (abstract) 218
- nitroglycerin dose-related effect on, intravenous 30
- serotonin effects on, during anesthesia 1163
- verapamil effects on, during pregnancy 7

**Book reviews**
- A Calculus of Suffering. Pain, Professionalism, and Anesthesia in Nineteenth Century America, Leroy D. Vandam 1229
- A Practice of Anaesthesia, Carol L. Lake 655

**Book reviews**—*continued*
- Cardiovascular Anesthesia, William A. Lell, A. J. Wright 1039
- Clinical Anesthesia in Neurosurgery, Mai-Li Dong 560
- Clinical Transcutaneous Electric Nerve Stimulation, Lorne G. Eltherington 848
- Computing in Anesthesia and Intensive Care, J. Robert Boston 183
- Current Concepts in Regional Anaesthesia, Gale E. Thompson 464
- Endocrinology and the Anaesthetist, Arthur J. Klowden 1039
- Manual of Anesthesia, 2nd ed., James K. Alifimoff 655
- Manual of Cardiac Anesthesia, Fred Koch 560
- Nitrous Oxide/N$_2$O, Jeffrey B.Gross 1230
- Plexus Anesthesia, Volume I, Perivascular Techniques of Brachial Plexus Block, Gale E. Thompson 654
- Post-anasethetic recovery, Mahmood Tabatabai 94
- Quality of Care in Anaesthetic Practice, E. S. Siker 464
- The Kidney in Anesthesia, Lee H. Cooperman 848
- The Year Book of Critical Care Medicine, Robert R. Kirby 654
- Understanding Anesthesia Equipment, 2nd ed., Robert E. Binda Jr. 655

**Brain**
- acetylcholine, synthesis and release of 385, 395
- blood flow
  - anatomy of 143
  - anesthetic metabolism and 143
  - metabolic effects of midazolam on 129
  - regulation of 143
- catecholamines
  - central serotonin depletion effects on 1163
- death
  - organ donors with, hemodynamic responses of 125
  - surgically induced hypertension with (letter) 1030
- electroencephalography (letter) 646
- evoked responses
  - (abstract) 242, 285
  - fentanyl and alfentanil effect on 597
  - isoflurane and isoflurane–nitrous oxide effects on 43
- intracranial pressure
  - atracurium as cause
    - (abstract) 249, 257
    - neurosurgical patients and 1113
    - diltiazem effect on 1001
    - (abstract) 291
    - in neuroanesthesia principles 143
- ischemia, intravenous glucose solution effects on (letter) 558
- pituitary, in opiate analgesia 781
- protection of, during neuroanesthesia 143
- serotonin
  - blood pressure control and 1163
  - sufentanil effects on, in halothane anesthesia 857
- stroke, metocurine sensitivity with 767

**Bupivacaine,** see Anesthetics, local

**Buprenorphine,** see Analgesics

**Burns,** see Complications

**Butorphanol,** see Analgesics

**Caffeine,** see Analeptics

**Calcium,** see Ions

**Capnography,** see Measurement techniques, carbon dioxide

**Carbon dioxide**
- absorber for, condensation chamber of 541
- end-tidal
  - malignant hyperthermia detection and monitoring with 837
  - venous air embolism detection by 688
- hypocarbia, myocardial circulation and (letter) 462

**Cardiopulmonary bypass,** see
- Anesthesia, cardiovascular
- Surgery, cardiovascular

**Cardiovascular anesthesia,** see Anesthesia

**Catecholamines,** see
- Brain
- Sympathetic nervous system

**Catheterization, cardiac,** see Heart

**Catheters,** see Equipment

**Cerebrospinal fluid**
- distribution of local anesthetics in 715
- $\beta$-endorphin clearance from (letter) 180

**Cesarean section,** see Anesthesia, obstetric

**Children,** see Anesthesia, pediatric

**2-Chloroprocaine,** see Anesthetics, local

**Chymopapain,** see Allergy

**Cimetidine,** see
- Gastrointestinal tract, antacids
- Pharmacology

**Ciramadol,** see Analgesics

**Circuits, anesthetic,** see Equipment

**Cirrhosis,** see Liver

**Citrate,** see Gastrointestinal tract, antacids

**Coagulation,** see Blood

**Cocaine,** see Anesthetics, local

**Complications**
- aspiration
  - antacid pretreatment for prevention of, in cesarean section 34
- asthma 551
- burns, fires
  - surgical drapes contributing to, flammable 54
  - thiopental requirements for children after 1156
- croup and epiglottitis 621
- dysautonomia, familial 72
- misidentification of drugs (letter) 179
- Moebius syndrome 371
- myoclonus, etomidate recovery with 80 (letter) 943
- myotonic dystrophy, with atracurium 369
- paralysis, diaphragmatic 1208
- paraplegia
  - pancuronium and neostigmine effects 864
  - spinal angioma causing, with epidural analgesia association 937
- pneumothorax, from adhesive plastic drape (letter) 462
- priapism, ketamine treatment of (letter) 1033
- risk, sensitive measures of outcome and (letter) 751
- shivering (abstract) 235
- spinal fusion (letter) 843
- subarachnoid hemorrhage 86
- trigeminal nerve palsy (letter) 653

**Computer programs**
- for anesthetic record retrieval 425
- for sodium nitroprusside infusion regulation 38

**Croup,** see Larynx, edema

**Curare,** see Neuromuscular relaxants, *d*-tubocurarine

**Dantrolene,** see
- Hyperthermia, malignant
- Neuromuscular relaxants

**Diazepam,** see Hypnotics, benzodiazepines

**Diltiazem,** see
- Heart, arrhythmias
- Pharmacology

**Droperidol,** see Anesthetics, intravenous

***d*-tubocurarine,** see Neuromuscular relaxants

**Dysautonomia,** see Complications

**Edrophonium,** see Antagonists, neuromuscular relaxants

**Education**
- B. B. Sankey Anesthesia Advancement Award 657
- subjective evaluation of textbooks in 362

**Electrical systems**
- fires from, flammable surgical drapes in 54

**Electrocardiography,** see Heart

**Electroconvulsive therapy,** see Anesthesia, electroshock

**Electroencephalography,** see
- Brain
- Monitoring

**Embolism**
- air
  - (abstract) 253
  - pulmonary artery pressure, carbon dioxide and nitrogen analysis for detection of 688
- starch, high-frequency oscillatory ventilation and 1041

**Endarterectomy,** see Surgery

**Endorphins,** see Polypeptides

**Endotracheal tubes,** see Equipment

- **Enflurane,** see Anesthetics, volatile
- **Enzymes**
  - adenylate cyclase, halothane effect on 531
  - methionine synthetase, nitrous oxide inactivation of 465
  - pseudocholinesterase, deficiency of (letter) 557
- **Epidural anesthesia,** see Anesthetic techniques
- **Epiglottitis,** see Complications
- **Epinephrine,** see
  - Heart, arrhythmias
  - Sympathetic nervous system
- **Equipment**
  - absorbers, carbon dioxide 541
  - catheters
    - arterial (letter) 844
    - epidural 1205
  - circuits
    - (abstract) 271
    - closed, gas contamination of 343
  - electric shock injuries from (letter) 559
  - endotracheal tubes (letter) 1030
  - exhaust systems (letter) 378
  - humidifiers (letter) 1224
  - nebulizer, for nasal administration of drugs 739
  - nerve stimulator 1217
    - (abstract) 256
  - pH sensor, for continuous intravascular measurements 731
  - preoperative check of (abstract) 264
  - pressurized infusion systems
    - for fluid resuscitation 382
    - (letter) 458
  - stethoscope amplifier, esophageal (letter) 377
  - surgical drapes, flammable 54
  - valves
    - directional (abstract) 237
    - dome, incompetent unidirectional 745
  - vaporizers, isoflurane 634
  - ventilators
    - (abstract) 246
    - bellow's leak in (letter) 942
- **Esmolol,** see
  - Heart
  - Sympathetic nervous system
- **Etomidate,** see
  - Anesthetics, intravenous
  - Induction, anesthesia
- **Evoked potentials,** see
  - Brain
  - Monitoring
- **Eye**
  - intraocular pressure
    - (abstract) 245
    - anesthesia effects on 520
    - physiologic determinants of 520
    - tracheal intubation-induced, lidocaine effect on 1211
- **Fentanyl,** see
  - Analgesics
  - Anesthetics, intravenous
- **Fires,** see
  - Complications
  - Electrical systems
  - Equipment
- **Fluid balance**
  - albumin, crystalloid, hydroxyethyl starch 753
- **Fluorocarbons,** see
  - Blood
  - Pharmacology
- **Fluosol,** see
  - Blood
  - Pharmacology
- **Gases, nonanesthetic**
  - contamination of closed-circuit anesthesia with 343
  - nitrogen, end-tidal analysis in detection of venous air embolism 688
- **Gastrointestinal tract**
  - antacids
    - cimetidine, sinus arrest associated with 453, 554
    - citrate pretreatment for cesarean section 34
    - radiotelemetric assessment of effect of, during labor 95
  - blood flow, fentanyl and morphine effects on 577
  - gastric pH and volume
    - age-related risk of pulmonary aspiration as indicated by 11
    - citrate pretreatment for cesarean section and 34
  - stomach
    - barotrauma case report and theoretical considerations 1026
- **Genetic factors**
  - pseudocholinesterase deficiency (letter) 557
- **Geriatric,** see
  - Age factors
  - Anesthesia, geriatric
- **Halothane,** see Anesthetics, volatile
- **Heart**
  - $\beta$-adrenoceptor blockade assessment during anesthesia 305
  - arrhythmias
    - cimetidine-induced sinus arrest 453
    - bretylium treatment of 911
    - bupivacaine causing 1089
    - diltiazem effect 964
      - (abstract) 236
      - halothane anesthesia and 964
    - hypocarbia and (letter) 462
    - isoflurane effect 570
    - lidocaine effect 911, 1089
    - respiratory sinus, in isoflurane–nitrous oxide anesthesia 811
      - venous cannulation as cause 1214
    - verapamil prevention of 1202
  - calcium ion effects on 432
  - cardiac arrest, with anterior mediastinal mass 1129
  - cardiac output
    - (abstract) 262
    - measurements of (letter) 652
  - catheterization effect on 1214
    - (abstract) 288
    - (letter) 844
  - conduction systems, enflurane and halothane effects on 1060
  - congenital defects
    - inhalational anesthetic induction in children with 101
    - patent ductus arteriosus 1078
  - electrocardiography, prolonged QT interval syndromes, 612
  - esmolol effects (abstract) 217, 238
  - ischemia
    - isoflurane anesthesia effects on 570
    - obstruction of aortocoronary bypass graft causing 933
    - subarachnoid hemorrhage and ECG changes simulating 86
    - verapamil for nitroglycerin-refractory, intraoperative 68
  - halothane effects 1149
  - isoproterenol effects 305
  - myocardial function
    - (abstract) 297, 303
    - $\beta$-adrenergic blockade effect 327
    - bupivacaine electrophysiologic and hemodynamic effects on 388
  - pancuronium effects 693
  - verapamil effects
    - (abstract) 198
    - in pregnancy 7
    - intraoperative use, for myocardial ischemia 68
- **Heparin,** see Blood, coagulation
- **Hepatitis,** see Liver
- **Hepatoroxdcity,** see Liver
- **Histamine**
  - trimethaphan-induced hypotension and blood levels of (abstract) 218
- **Hormones**
  - halothane and enflurane effects on, with hypertension 136
  - insulin, enflurane effects on secretion rates of 18
  - somatostatin, for postoperative pain 1085
- **Hydroxyzine,** see Hypnotics
- **Hypertension,** see Blood pressure
- **Hyperthermia**
  - malignant
    - (abstract) 300, 301
    - dantrolene therapy for 601
    - etomidate induction with 420
    - incidence of, in Denmark 700
    - mass spectroscopy detection and monitoring of 837
    - vecuronium effects on 515
    - verapamil as therapeutic adjunct for 601
- **Hypnotics**
  - barbiturates
    - methohexital
      - sedation of children for CT scan 643
      - termination of pregnancy with 792

**Hypnotics**—*continued*
- benzodiazepines
  - diazepam, autonomic tone deprivation and effects of 1053
  - lorazepam
  - aminophylline as antagonist of 834
  - hemodynamic effects (abstract) 228
- midazolam
  - (abstract) 186, 224, 272
  - ethanol interactions and reversal of 129
  - (letter) 1223
  - termination of pregnancy with 792
- hydroxyzine, potentiation of metoclopramide effects with (letter) 1227

**Hypobaria**
- altitude, in closed circuit anesthetic techniques (letter) 843

**Hypocarbia,** see Carbon dioxide

**Hypotension,** see
- Blood pressure
- Position
- Shock

**Hypothermia**
- anesthetic, temperature and ventilation after 816

**Hypoxia**
- hepatotoxicity with halothane and enflurane 955
- postoperative, pulse oximetry measurement of 1108

**Induction**
- anesthesia
  - circulatory shunts and 101
  - etomidate
    - malignant hyperthermia and 420
    - thiopental vs 871
  - fentanyl 48
  - fluosol effect 405
  - halothane vs enflurane for 77
  - intracranial hypertension and 143
  - ketamine dose–response curves for 795
  - midazolam dose–response curves for 795

**Infections**
- croup in children 621
- epiglottitis in children 621
- herpes virus, hepatic necrosis from 1131
- tetanus, dantrolene use in 538

**Insulin,** see Hormones

**Interactions (drug)**
- caffeine–morphine 851
- midazolam–ethanol 129
- vecuronium–*d*-tubocurarine 711

**Intracranial pressure,** see Brain

**Intraocular pressure,** see Eye

**Intravenous anesthesia,** see
- Anesthetic techniques
- Anesthetics, intravenous

**Intubation, tracheal**
- atomizer modification for nasal administration of drugs with 739
- blind (letter) 651
- lidocaine as suppressant of coughing during 1189
- neck movement affecting endotracheal tube position (letter) 1030
- translaryngeal guided (letter) 650

**Ions**
- calcium
  - (abstract) 203
  - cardiac and peripheral vascular actions of 432
  - heparin- and protamine-induced hypotension and 1081
- magnesium
  - (abstract) 202
  - vecuronium interaction 1220
- potassium
  - (abstract) 189, 192, 193
  - succinylcholine-induced increases in 1202

**Isoflurane,** see Anesthetics, volatile

**Isoproterenol,** see Heart

**Ketamine,** see
- Anesthetics, intravenous
- Induction, anesthesia
- Pharmacology

**Kidney**
- transplantation, morphine kinetics in 1065

**Labor,** see Anesthesia, obstetric

**Larynx**
- edema, with croup and epiglottitis 621
- spasm, lidocaine prevention after extubation 1193

**Laser,** see Surgery, otolaryngologic

**Lidocaine,** see
- Anesthetics, intravenous
- Anesthetics, local

**Lithotripsy,** see Surgery, urologic

**Liver**
- adenylate cyclase of, halothane effect on 531
- biliary tract, narcotics and (letter) 379
- cirrhosis, volatile anesthetics or fentanyl effects on 1183
- hepatitis
  - enflurane, nitrous oxide–narcotic, and spinal anesthesia with 487
  - epidemiology of, in anesthesia residents 672
  - isoflurane anesthesia with (letter) 458
- hepatotoxicity
  - halothane causing 465
  - enflurane vs 955
  - sex differences 563
- necrosis, from herpes virus 1131
- transplantation
  - anesthesia for 108, 117
  - blood coagulation changes and thromboelastographic monitoring during 888
  - orthotopic pediatric 117

**Local anesthetics,** see Anesthetics, local

**Lorazepam,** see Hypnotics, benzodiazepines

**Lung**
- aspiration
  - (abstract) 244
  - gastric pH and volume in age-related risk of 11
- asthma, low-pressure chamber and oxygen treatment of 551
- atelectasis, with one-lung ventilation 946
- blood flow
  - fentanyl effect on stress response in pulmonary circulation 1137
  - in one-lung ventilation 821, 946
- edema, high-frequency oscillatory ventilation and 1041
- hemorrhage, ventilatory management of 742
- pneumothorax, from adhesive plastic drape (letter) 462
- pulmonary artery
  - catheterization (letter) 844
  - pressure in venous air embolism detection 688
- shunting, with one-lung ventilation 946
- tracheoesophageal fistula, repair of 748
- water content, extravascular
  - (abstract) 243
  - colloid and crystalloid solution effects on, after surgery 753
  - high-frequency oscillatory ventilation and 1041
  - resuscitation after shock and 323

**MAC,** see Potency, anesthetic

**MAO inhibitors,** see Ataractics

**Magnesium,** see Ions

**Malignant hyperthermia,** see Hyperthermia

**Measurement techniques**
- blood pressure
  - (abstract) 206
  - during internal mammary artery dissection 1134
- carbon dioxide
  - absorbers 541
  - malignant hyperthermia detection via 837
  - venous air embolism detection via 688
- cardiac output (letter) 652
- high-performance liquid chromatography, for atracurium determination 58
  - mass spectroscopy, for malignant hyperthermia detection and monitoring 837
- oximetry, pulse
  - (abstract) 292
  - patient transfer to recovery room with 1108
  - pulmonary artery surgery with 376
- oxygen
  - on-line conjunctival tension, as guide to cerebral oxygenation 63
  - transcutaneous (abstract) 200, 294
- sympathetic activity measurement 415
- skin blood flow measurement (letter) 179

**Memory**
- intraoperative 1143

**Meperidine,** see Analgesics

**Metabolism**
- adenosine monophosphate, enflurane effects on 18
- glucose, during surgery (letter) 558

**Methionine synthetase,** see Enzymes

**Methohexital,** see
- Anesthetics, intravenous
- Hypnotics, barbiturates

**Methoxyflurane,** see Anesthetics, volatile

**Metocurine,** see Neuromuscular relaxants

**Midazolam,** see
- Anesthetics, intravenous
- Hypnotics, benzodiazepines
- Induction, anesthesia

**Moebius syndrome,** see Complications

**Monitoring**
- blood pressure
  - (abstract) 247
  - cardiovascular anesthesia 1134
- EEG (letter) 646
- end-tidal gases, for venous air embolism detection 688
- pH, intravascular, with fiberoptic sensor 731

**Morphine,** see
- Analgesics
- Anesthetics, intravenous

**Myoclonus,** see Complications

**Myotonic dystrophy,** see Complications

**Nalbuphine,** see Analgesics

**Naloxone,** see Antagonists, narcotics

**Neonate,** see
- Anesthesia, obstetric
- Anesthesia, pediatric

**Neostigmine,** see Antagonists, neuromuscular relaxants

**Nerve**
- peripheral, analgesic effects on 667
- stimulator 1217
  - (abstract) 256

**Neuromuscular relaxants**
- atracurium
  - coronary artery disease and pharmacology of (abstract) 191
  - degradation of, in plasma (abstract) 289
  - edrophonium and neostigmine antagonism of 867
  - enzymatic hydrolysis of (abstract) 261
  - halothane MAC with (abstract) 282
  - hemodynamic effects of, during sufentanil anesthesia (abstract) 295
  - high-performance liquid chromatography determination of 58
  - inactivation of, in plasma 1047
  - infusion requirements during halothane, isoflurane, and narcotic anesthesia 471
  - intracranial pressure after 1113
    - (abstract) 247, 257
    - in neurosurgical patients 1113
  - laudanosine as metabolite of (abstract) 232
  - myotonic dystrophy and 369
  - neuromuscular and circulatory responses with fentanyl (abstract) 284
  - pancuronium combined with (abstract) 259
  - pharmacodynamics and pharmacokinetics (abstract) 207
  - pheochromocytoma and 547
  - succinylcholine-induced fasciculations and postoperative myalgia with 1010
  - receptor kinetics of 777
  - respiratory effects of (abstract) 226
  - single twitch and train-of-four responses (abstract) 187
  - single vs divided doses of (abstract) 298
- BW B1090U (abstract) 278
- cost of (letter) 943
- dantrolene
  - for malignant hyperthermia 601
  - for severe tetanus 538
- metocurine
  - (abstract) 252
  - decreased sensitivity to, with upper motoneuron disease 767
  - neurosurgical patients for studies of (letter) 846
  - pharmacokinetics and pharmacodynamics of, in elderly 23
- monitoring of (abstract) 225
- non-depolarizing, hemodynamic comparison of, (abstract) 287
- pancuronium
  - (abstract) 252, 259
  - anaphylactoid reaction to (letter) 944
  - cardiac electrophysiologic effects of 693
  - fasciculations with (letter) 557
  - fentanyl anesthesia induction with 48
  - resistance to, in adult respiratory distress syndrome 1126
  - response differences in hemiplegic patients 864
  - sufentanil anesthesia with (abstract) 295
  - verapamil potentiation of neuromuscular blockade by 1021
- succinylcholine
  - (abstract) 188, 265
  - fasciculations induced by, atracurium for 1010
  - neostigmine antagonism of 773
  - requirements for stable mechanical effect 319
  - verapamil effect on potassium increases induced by 1202
- *d*-tubocurarine
  - neurosurgical patients for studies of (letter) 846
  - pharmacokinetics and pharmacodynamics of, in elderly 23
  - sensitivity of limb muscles to 1178
  - vecuronium combination with 711
  - verapamil potentiation of neuromuscular blockade by 1021
- vecuronium
  - (abstract) 187, 212, 295
  - infusion dose requirements during fentanyl and halothane anesthesia 411
  - magnesium sulfate interaction with 1220
  - malignant hyperthermia and 515
  - requirements for stable mechanical effect 319
  - tubocurarine combination with 711

**Neuromuscular transmission**
- verapamil and EGTA effects on 505

**Nifedipine,** see Pharmacology

**Nitroglycerin,** see
- Anesthetic techniques, hypotensive
- Pharmacology

**Nitroprusside,** see Anesthetic techniques, hypotensive

**Nitrous oxide,** see Anesthetics, gases

**Obituary**
- Griffith, Harold R. 945

**Opioids,** see
- Analgesics
- Anesthetics, intravenous

**Oximetry,** see Measurement techniques

**Oxygen measurements**
- on-line conjunctival, as guide to cerebral oxygenation 63
- postoperative blood levels of, measurement of 1108

**Pain**
- postoperative
  - ciramadol for, morphine and placebo comparison 1101
  - ketamine for, epidural 1161
  - lidocaine for, intravenous continuous low-dose 971
  - morphine for, epidural 786
  - somatostatin effect on, epidural 1085

**Pancuronium,** see Neuromuscular relaxants

**Paraplegia,** see Complications

**Pediatrics,** see Anesthesia, pediatric

**PEEP,** see Ventilation, positive end-expiratory pressure

**Peptides,** see Polypeptides

**Peridural,** see Anesthetic techniques, epidural

**pH,** see
- Acid–base equilibrium
- Carbon dioxide
- Gastrointestinal tract, antacids

**Pharmacodynamics**
- metocurine and tubocurarine in elderly 23

**Pharmacokinetics**
- aminophylline, anesthetic effects on (letter) 460
- circulatory shunt effects 101

**Pharmacokinetics**—*continued*

- fentanyl, in preterm infants during cardiac surgery 1078
- halothane 1171
- inhalation anesthetics (abstract) 197
- isoflurane 1171
- metocurine, in elderly 23
- morphine, in kidney transplantation 1065
- tubocurarine in elderly 23

**Pharmacology**

- aminophylline
  - fentanyl anesthesia antagonism (letter) 1034
  - lorazepam antagonism 834
- cimetidine, sinus arrest associated with 453, 554
- diltiazem
  - (abstract) 291
  - antiarrhythmic effect during halothane anesthesia 964
  - intracranial pressure during hypotension induced by 1001
- fluorocarbons, fluosol, in inhalation anesthesia induction 405
- ketamine, priapism treatment with (letter) 1033
- nifedipine (abstract) 222
- nitroglycerin, dose-related prolongation of bleeding time with 30
- protamine 348
- vecuronium and magnesium sulfate interaction 1220
- verapamil
  - (abstract) 216, 248
  - as dantrolene adjunct for malignant hyperthermia 601
  - neuromuscular blockade potentiation with 1021
  - phrenic nerve-hemidiaphragm preparation with 505
  - uterine blood flow and maternal cardiovascular function 7

**Pheochromocytoma,** see Neuromuscular relaxants, atracurium

**Pituitary,** see

- Brain
- Surgery, neurologic

**Pneumothorax,** see Lung

**Polypeptides**

- $\beta$-endorphin
  - (abstract) 210
  - central serotonin depletion effect on 1163
  - cerebrospinal fluid clearance of (letter) 180
  - halothane and fentanyl anesthesia effects on 677
- renin-angiotensin
  - central serotonin depletion effect on 1163
  - in halothane and enflurane responses with hypertension 136

**Position**

- endotracheal tube, neck movement effects on (letter) 1030
- hemodynamic effects (abstract) 194

**Potassium,** see Ions

**Potency, anesthetic**

- MAC
  - halothane
    - in isoflurane comparison 381
    - in morphine–alfentanil comparison 807
  - MAPP vs (letter) 646

**Pregnancy**

- abortion
  - hospitalization for, among Swedish nurses working in operating rooms 981
  - midazolam vs methohexital for 792

**Priapism,** see Complications

**Proglumide,** see Antagonists, miscellaneous

**Protamine,** see Blood, coagulation

**Pseudocholinesterase,** see Enzymes

**Psychologic tests**

- postanesthetic (letter) 182

**Publications**

- anesthesia journals, statistical methods in 607

**Pulmonary,** see Lung

**Records**

- anesthesia, computerized system for 425

**Recovery**

- psychomotor tests (letter) 182

**Renin,** see Polypeptides

**Research**

- B. B. Sankey Anesthesia Advancement Award 657

**Risk**

- sensitive measures of outcome and (letter) 751

**Serotonin,** see Brain

**Shivering,** see Complications

**Shock**

- resuscitation after, extravascular lung water with 323

**Shoulder block,** see Anesthetic techniques, regional

**Shunt,** see

- Anesthesia, cardiovascular
- Lung
- Heart
- Oxygen
- Surgery, neurologic
- Ventilation

**Skin**

- blood flow, measurements of (letter) 179

**Solubility**

- fluosol, partition coefficients in 405
- temperature and age effects on anesthetics in blood 640
- volatile anesthetic, in ovine tissues 1097

**Somatostatin,** see Hormones

**Spinal anesthesia,** see Anesthetic techniques, spinal

**Spinal cord**

- blood flow (abstract) 240

**Statistics**

- common sense in (letter) 1035
- computerized system for anesthetic record retrieval 425
- descriptive and correlative 561
- methods, evaluation of 670
- p valves and (letter) 559

**Stethoscope,** see Equipment

**Stomach,** see Gastrointestinal tract

**Stroke,** see Brain

**Subarachnoid hemorrhage,** see Complications

**Succinylcholine,** see Neuromuscular relaxants

**Sufentanil,** see Anesthetics, intravenous

**Surgery**

- cardiovascular
  - (abstract) 283
  - aortocoronary bypass graft obstruction by intraoperative positioning 933
  - bronchial hemorrhage with 742
  - colloid and crystalloid solution effects after 753
  - hypothermic, temperature and ventilation after 816
  - pulse oximetry during 376
  - verapamil for myocardial ischemia during 68
- endarterectomy (abstract) 195
- neurologic
  - chymopapain anaphylaxis 1197
  - muscle relaxant studies during (letter) 846
  - subarachnoid hemorrhage and ECG changes of myocardial ischemia with 86
- orthopedic
  - posterior spinal fusion for kyphoscoliosis 83
  - shoulder reconstruction, regional anesthesia for 373
- otolaryngologic, laser (letter) 1037
- replantation
  - knowledge and clinical competency skills (letter) 90
  - one-lung ventilation in 821, 946
- urologic
  - extracorporeal shock wave lithotripsy 544
  - nephrolithotomy 840
  - transurethral prostatectomy 1071

**Sympathetic nervous system**

- $\beta$-adrenergic receptors
  - antagonists at 327
  - blockade assessment during anesthesia 305
- catecholamines
  - central serotonin depletion effect on 1163

- in halothane and enflurane responses with hypertension 136
- morphine and fentanyl infusion effects on, during surgery 509
- complete blockade of, signs of 415
- epinephrine
  - hemodynamic and plasma catecholamine responses to 924
- esmolol, cardiovascular effects 327
- halothane effects 1

**Temperature**
- body
  - (abstract) 267
  - after cardiovascular anesthesia 816
  - postoperative (abstract) 213
  - volatile anesthetic solubility effects of 640

**Tetanus,** see
- Infections
- Neuromuscular relaxants

**Theophylline,** see Pharmacology, aminophylline

**Thiopental,** see Anesthetics, intravenous

**Toxicity**
- ammonia 1071
- benzyl alcohol (letter) 559
- bupivacaine 911
- glycine, in transurethral resection syndrome 1071
- halothane, enflurane, and methoxyflurane comparison 1005
- local anesthetic 1089
  - (abstract) 204
  - (letter) 844
- protamine 348
  - (letter) 1033
- trace anesthetic concentrations as cause 981

**Transcutaneous,** see
- Measurement techniques
- Nerve, stimulator

**Transfusion**
- plasma, fresh frozen 849

**Transplantation,** see specific organs

**Trimethaphan,** see Anesthetic techniques, hypotensive

**Tubocurarine,** see Neuromuscular relaxants

**Uterus**
- blood flow, verapamil effects on 7

**Valves,** see Equipment

**Vaporizers,** see Equipment

**Vecuronium,** see Neuromuscular relaxants

**Veins**
- cannulation
  - arrhythmias during 1214
  - guide wire complication during (letter) 460
- venipuncture, counter-irritation techniques during (letter) 379

**Ventilation**
- artificial, high-frequency 1041
- one-lung 821
  - isoflurane and halothane anesthesia with 946
  - optimization of oxygenation during (letter) 1036
  - single unit device for, with one anesthesia machine 1017
- positive end-expiratory pressure (abstract) 201

**Ventilators,** see Equipment

**Verapamil,** see
- Heart
- Pharmacology

# Anesthesia and Analgesia

## BACK ISSUES AVAILABLE

Available at $3.00 per Issue

| Vol. | Year | Numbers Available | | | | | | Vol. | Year | Numbers Available | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 33 | 1954 | – | 2 | 3 | 4 | 5 | 6 | 41 | 1962 | – | 2 | 3 | – | 5 | 6 |
| 34 | 1955 | 1 | 2 | 3 | 4 | 5 | 6 | 42 | 1963 | – | – | 3 | 4 | 5 | 6 |
| 35 | 1956 | 1 | 2 | 3 | – | 5 | 6 | 43 | 1964 | 1 | – | 3 | – | 5 | 6 |
| 36 | 1957 | – | – | – | – | – | 6 | 44 | 1965 | 1 | 2 | 3 | 4 | 5 | 6 |
| 37 | 1958 | 1 | 2 | 3 | 4 | 5 | 6 | 45 | 1966 | – | 2 | – | 4 | 5 | 6 |
| 38 | 1959 | – | 2 | 3 | 4 | – | 6 | 46 | 1967 | – | 2 | 3 | 4 | – | 6 |
| 39 | 1960 | – | – | 3 | 4 | 5 | 6 | 47 | 1968 | – | – | 3 | 4 | 5 | 6 |
| 40 | 1961 | – | – | – | 4 | 5 | 6 | 48 | 1969 | 1 | 2 | 3 | – | 5 | – |

Available at $4.50 per Issue

| Vol. | Year | Numbers Available | | | | | | Vol. | Year | Numbers Available | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 49 | 1970 | 1 | – | – | – | 5 | 6 | 54 | 1975 | – | 2 | 3 | – | – | 6 |
| 50 | 1971 | 1 | 2 | – | – | – | – | 55 | 1976 | – | 2 | 3 | 4 | 5 | 6 |
| 51 | 1972 | – | 2 | 3 | – | – | 6 | 56 | 1977 | 1 | 2 | 3 | 4 | 5 | 6 |
| 52 | 1973 | 1 | 2 | 3 | 4 | 5 | 6 | 57 | 1978 | 1 | 2 | 3 | 4 | 5 | 6 |
| 53 | 1974 | – | 2 | 3 | 4 | – | – | | | | | | | | |

Available at $5.50 per Issue

| Vol. | Year | Numbers Available | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 58 | 1979 | 1 | 2 | 3 | 4 | 5 | 6 | (only six issues published) | | | | | |
| 59 | 1980 | – | – | 3 | 4 | 5 | 6 | – | 8 | 9 | 10 | 11 | 12 |
| 60 | 1981 | 1 | 2 | 3 | 4 | 5 | 6 | – | – | 9 | 10 | 11 | 12 |
| 61 | 1982 | 1 | 2 | 3 | 4 | 5 | 6 | – | – | 9 | 10 | 11 | 12 |

SINGLE ISSUES PRIOR TO 1954: Write to publisher at address below for listing of issues available at $2.00 each.

OTHER PUBLICATIONS AVAILABLE:
- "Basic and Clinical Physiology of the Liver" (Supplement to Sept.–Oct. 1965 issue)—$3.00.
- Ten-Year (1960–1969) Cumulative Index—$3.00.
- Ten-Year (1970–1979) Cumulative Index—$3.00.
- 1982 (56th Congress) Review Course Lectures—$5.00.
- 1983 (57th Congress) Review Course Lectures—$5.00.
- 1984 (58th Congress) Review Course Lectures—$6.00.
- 1985 (59th Congress) Review Course Lectures—$6.00.

International Anesthesia Research Society
3645 Warrensville Center Rd.
Cleveland, Ohio 44122

Please send me the publications circled above, or listed hereunder:

☐ Check for $_______ enclosed.

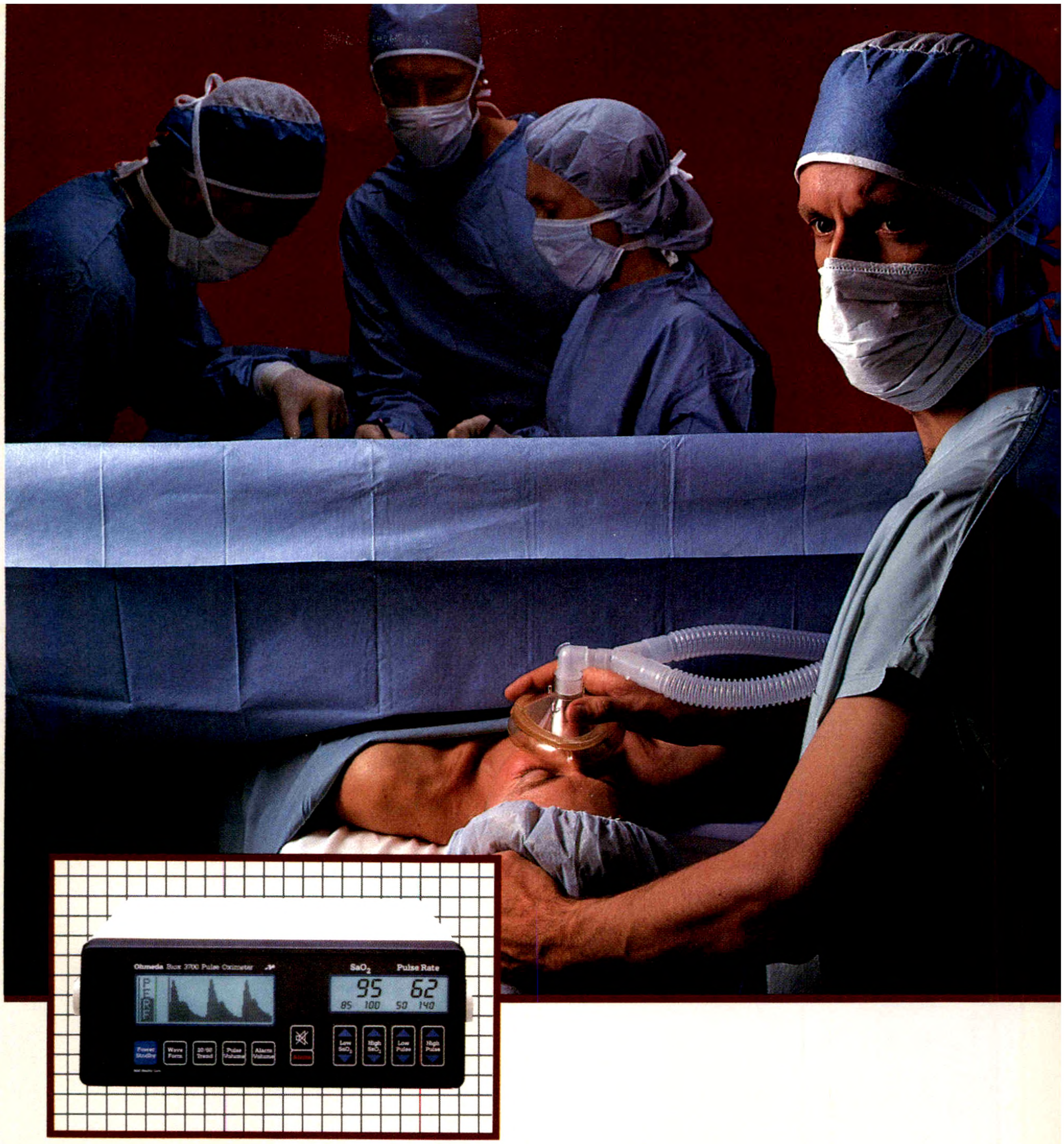
☐ Please send bill with understanding that ordered material will be sent when payment is received.

Name ______________________________

Address ______________________________

City, State, Zip ______________________________

Requests for single issues beginning with Vol. 62 should be sent to Elsevier Science Publishing Co, Inc., 52 Vanderbilt Avenue, New York, NY 10017.
Ten-Year Cumulative Index (1975–1984) is available only through Elsevier.



# The New Ohmeda Biox 3700 Pulse Oximeter. Because hypoxemia is an $SaO_2$ problem.

**Why oximetry.**

A drop in arterial blood oxygenation ($SaO_2$) calls for quick and effective action. Especially in anesthesia, where oxygen starvation can jeopardize your patient's safety. Only oximetry provides the means for direct and efficient monitoring of $SaO_2$—giving you the crucial time needed to prevent clinical complications.

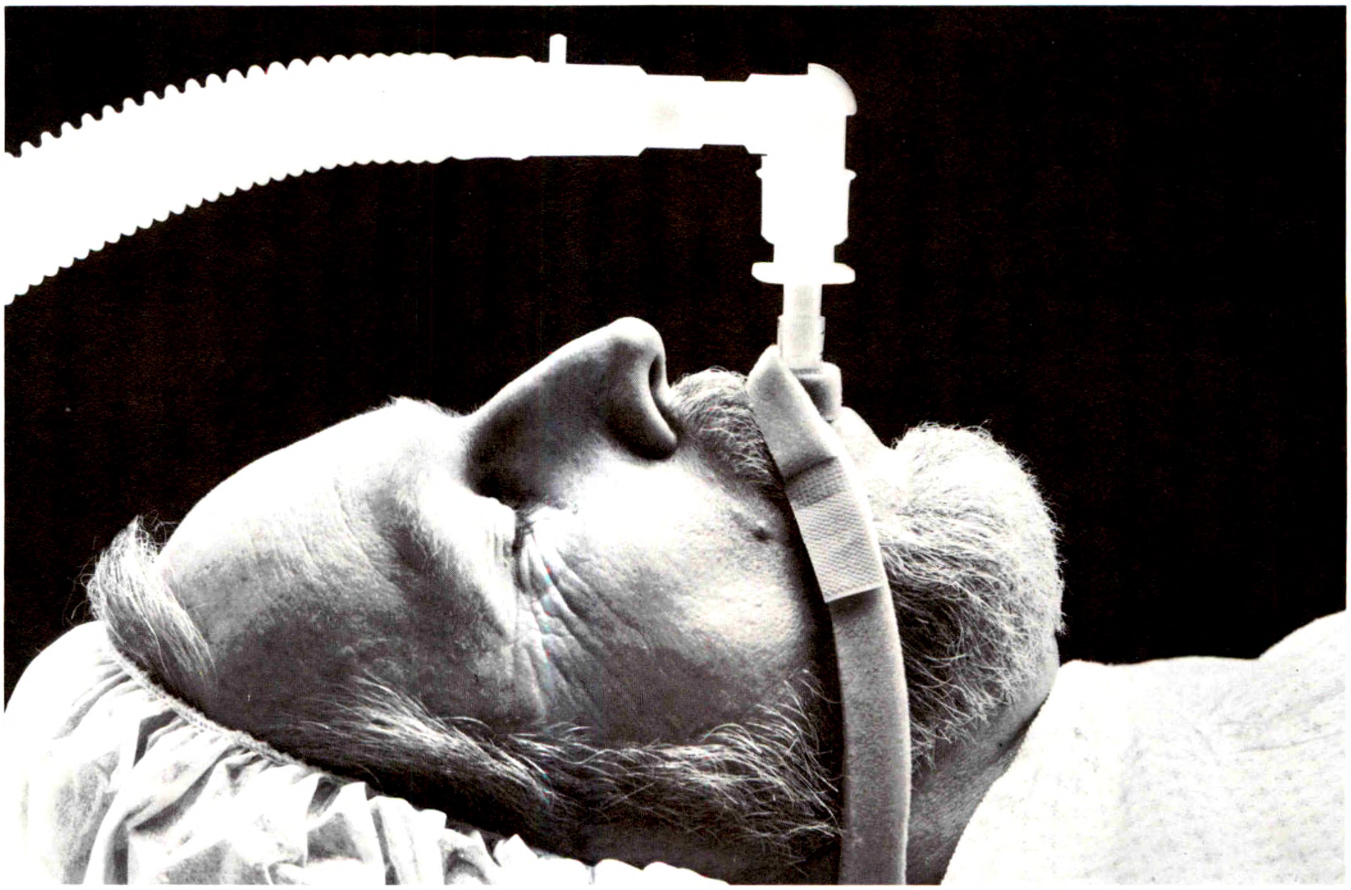
**Why Ohmeda.**

Now, the Ohmeda Biox 3700 Pulse Oximeter helps you in the prompt detection of hypoxemia. Continuous, reliable and non-invasive, only the 3700 shows you a plethysmographic waveform—plus $SaO_2$ trending of the past 20 or 60 minutes. Both visual and audible indicators continuously inform you of your patient's $SaO_2$ condition as you work. The 3700 has a battery backup, for easy transport and emergency power support. And its three types of probes make the 3700 ideally suited for any patient.

So, prevent minor procedures from becoming major hypoxic crises. Rely on the Ohmeda Biox 3700. It's the confident response to the critical demands of anesthesia.

**Ohmeda**

Ohmeda
4765 Walnut Street
Boulder, Colorado 80301 1 800 652 2469
A Division of The BOC Group, Inc.
**BOC Health Care**



# Introducing STRAPEZE™

## While others slip and slide all over the place, we've made a name for ourselves by staying put.

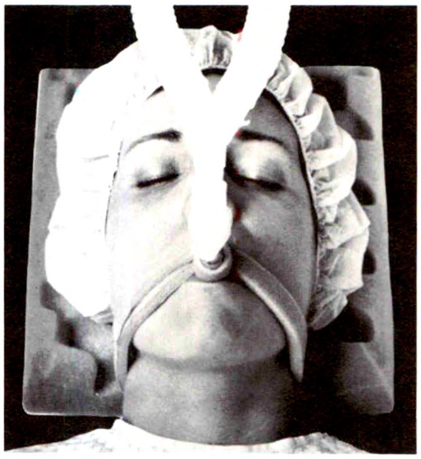
**No more fumbling for the tape. No more sticky adhesive devices. And no more concerns for the security and safety of your patient's airway. Now enjoy the speed, simplicity and protection of STRAPEZE.**

### Strap versus tape

Tape kinks, binds, and often loses its adhesive qualities under operating conditions. STRAPEZE, as its name implies, is a strap made of 100% non-allergenic Velfoam II®, a very durable and lightweight material with a foam core sandwiched between outer layers of soft, synthetic lambs-wool.

### So easy to apply

The STRAPEZE "one-step" fastening concept brings a new measure of assurance and security to endotracheal tube placement. And there's nothing else like it for ease of use. You simply attach one end of STRAPEZE to the tube, slip the strap behind the patient's neck, loop around tube and fasten with the Velcro tab back onto the strap's velvety surface. Job finished!



### Stays put—or it's not STRAPEZE!

Now you can forget about accidental extubations or bronchial intubations. STRAPEZE ensures precise and positive positioning of the tube. Where you put it, is where it stays. Which means the tube won't pull out, and it won't push down. Needless to say, such assurances can be a lifesaver.

### Another quality product from ProTechPacific

STRAPEZE was designed to answer the demanding needs of today's medical professional. Its innovative simplicity erases the tedium and uncertainty of performing an important task. And its specialized function is another example of ProTech Pacific's ongoing commitment to your profession. STRAPEZE. New convenience. New security. New comfort. And, for all these assurances, very inexpensive. For the comfort of the intubated patient, STRAPEZE is here to stay. Because it *stays put*.

*U.S. Patents pending*

**ProTechPacific**

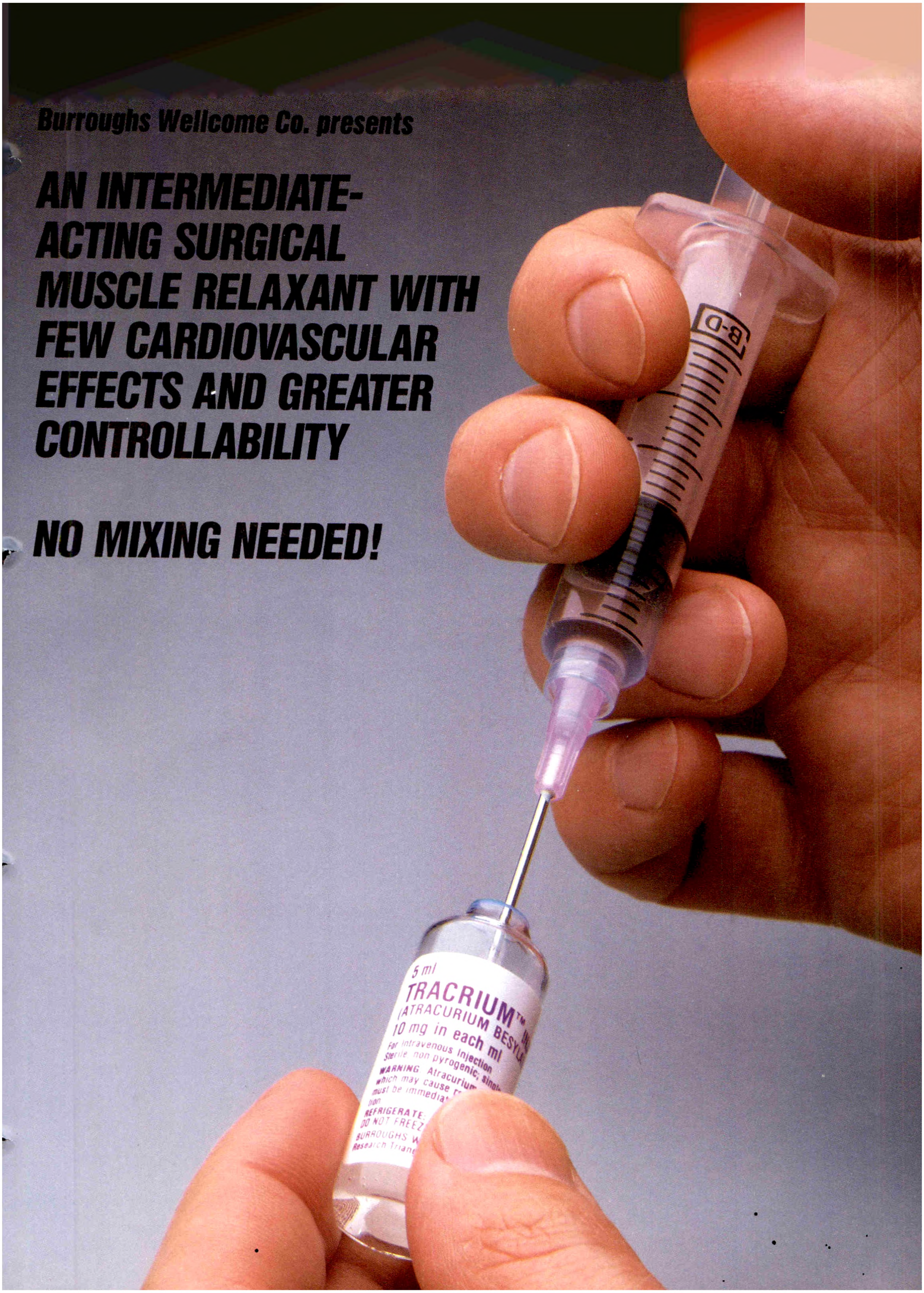
*1221 Andersen Drive*
*San Rafael, California 94901*
*Call Toll Free: 800/227-0517*
*In Calif. 415/459-0745*

*Manufacturers of Protective Medical Products*

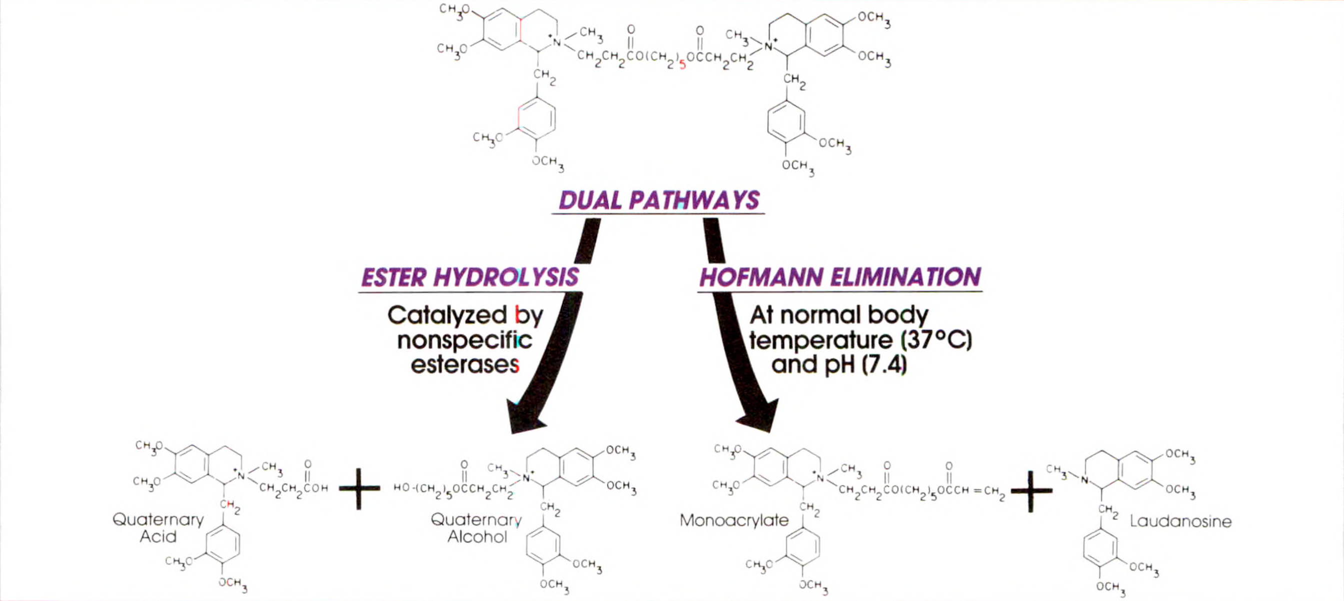
**Burroughs Wellcome Co. presents**

# AN INTERMEDIATE-ACTING SURGICAL MUSCLE RELAXANT WITH FEW CARDIOVASCULAR EFFECTS AND GREATER CONTROLLABILITY

## NO MIXING NEEDED!



# UNIQUE METABOLISM PROVIDES BETTER PREDICTABILITY, ALLOWING BETTER CONTROL



*☐ Tracrium® Injection (atracurium besylate) is inactivated by two nonoxidative pathways that are not dependent on kidney or liver function:*

*① Hofmann elimination—a nonenzymatic process that occurs at physiologic temperature and pH*

*② Ester hydrolysis—catalyzed by nonspecific esterases; normal levels of plasma cholinesterase are not required*

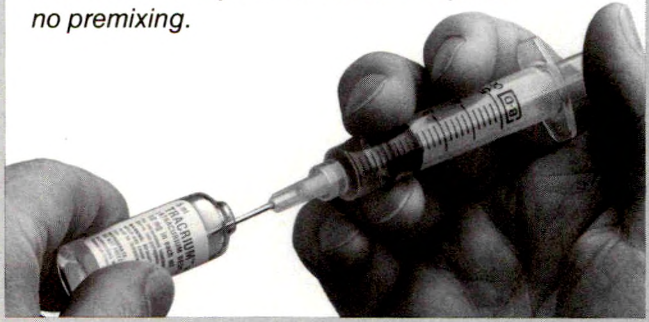
*These attributes make Tracrium a more flexible surgical muscle relaxant—it may be tailored to a wide variety of surgical cases.*

*"Atracurium has the special feature of being broken down to inactive products by the Hofmann elimination reaction. This means that the active drug can be removed from the biophase by other means not totally dependent on enzyme action, redistribution or excretion."[1]*

*"At present, no other available muscle relaxant undergoes this kind of degradation at physiologic pH."[2]*

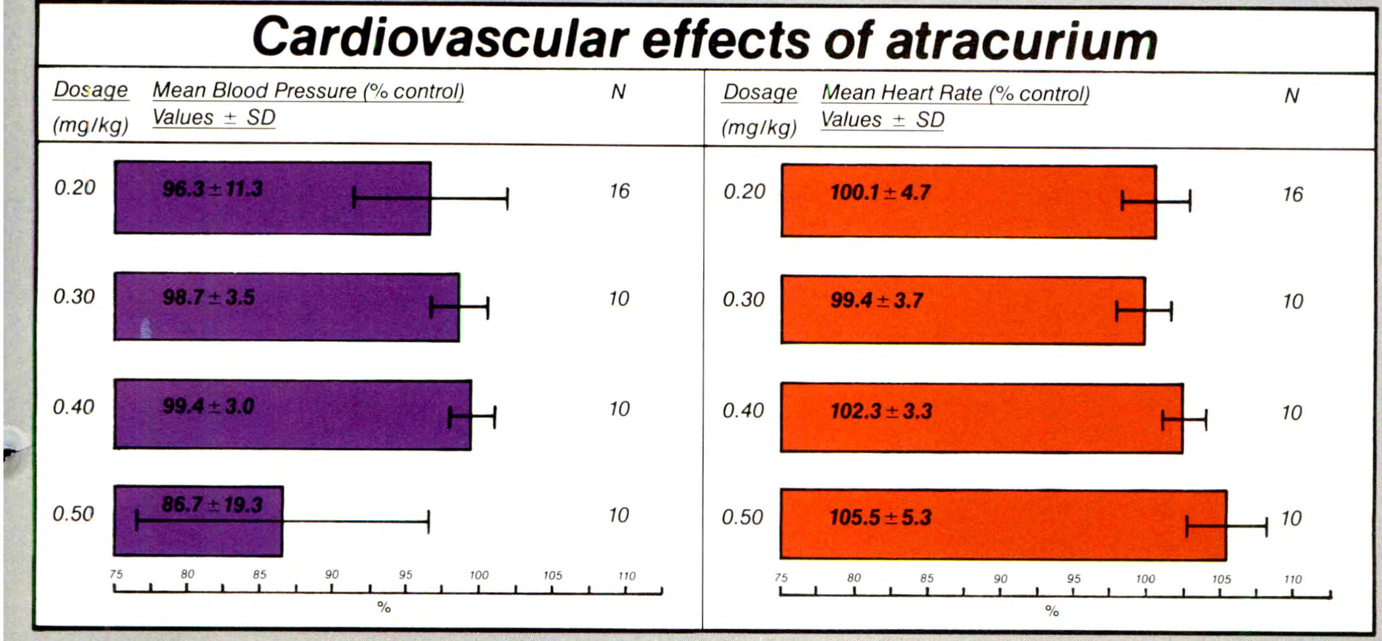
## Convenient and Ready to Use

*Tracrium is easily administered—requires no premixing.*



## Few Cardiovascular Effects at Recommended Dosages

*☐ Tracrium® (atracurium besylate) produces virtually no clinically significant cardiovascular hemodynamic changes when administered at recommended dosage levels—a significant benefit in patients with compromised cardiac ability or cardiac risk.*


Cardiovascular effects of atracurium

*Adapted from Basta et al.[3]*

## No Cumulative Effects Upon Recovery, After Multiple Doses

*☐ Repeated equipotent doses of Tracrium, administered at equal points of recovery, have no cumulative effect on recovery time*

*☐ Once recovery begins, it is relatively rapid and independent of dose*

*☐ This means that you do not have to calculate progressively smaller doses for repeat administration, and that recovery is more consistent and predictable*

*"One patient received 12 successive doses of atracurium after recovering completely from the initial dose, yet the 25%-75% recovery times were 10.0 and 12.2 min, respectively. This may indicate that atracurium is not cumulative. . . ."[1]*

## Minimal Histamine Release

*☐ Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine*

*☐ Clinically significant histamine release occurs well within the clinical dosage range (at $ED_{95}$) for curare, at the upper limits of the clinical dosage range (at 2 × $ED_{95}$) for metocurine and outside the clinical dosage range (at 3 × $ED_{95}$) for atracurium[4]*

*☐ The lack of hemodynamic changes due to Tracrium suggests minimal histamine release*

*Please see brief summary of prescribing information on the following page.*

*REFERENCES:*

*1. Ali HH, Savarese JJ, Basta SJ, et al: Clinical pharmacology of atracurium: A new intermediate acting nondepolarizing relaxant. Seminars in Anesthesia 1982; 1:57-62.*

*2. Katz RL, Stirt J, Murray AL, et al: Neuromuscular effects of atracurium in man. Anesth Analg 1982; 61:730-734.*

*3. Basta SJ, Ali HH, Savarese JJ, et al: Clinical pharmacology of atracurium besylate (BW 33A): A new non-depolarizing muscle relaxant. Anesth Analg 1982; 61:723-729.*

*4. Basta SJ, Savarese JJ, Ali HH, et al: Histamine-releasing potencies of atracurium besylate (BW 33A), metocurine, and d-tubocurarine. Anesthesiology 1982;57:A261.*

**TRACRIUM® INJECTION**
(atracurium besylate)

*Copr. ©1984 Burroughs Wellcome Co. All rights reserved.*

# TRACRIUM® INJECTION
## (atracurium besylate)

This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

**DESCRIPTION:** Tracrium (atracurium besylate) is an intermediate-duration, nondepolarizing, skeletal muscle relaxant for intravenous administration.

**INDICATIONS AND USAGE:** Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

**CONTRAINDICATIONS:** Tracrium is contraindicated in patients known to have a hypersensitivity to it.

**WARNINGS:** TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT.

DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

Tracrium has no known effect on consciousness, pain threshold, or cerebration. It should be used only with adequate anesthesia.

Tracrium Injection should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated.

**PRECAUTIONS:**

**General:** Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine. The possibility of substantial histamine release in sensitive individuals must be considered however. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute.

Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants.

Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome or other neuromuscular diseases or in patients with severe electrolyte disorders or carcinomatosis.

The safety of Tracrium has not been established in patients with bronchial asthma.

**Drug Interactions:** The neuromuscular blocking action of Tracrium may be enhanced by enflurane; isoflurane; halothane; certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; or quinidine.

**You'll get the latest facts on**
**TRACRIUM® INJECTION**
**(atracurium besylate)**
**at**
**The New York State**
**Society of Anesthesiologists**
**PGA in Anesthesiology**

**New York, NY**
**December 14-17, 1985**

If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered.

Prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Carcinogenesis and fertility studies have not been performed. Atracurium was evaluated in a battery of three short term mutagenicity tests. It was non-mutagenic in both the Ames Salmonella assay at concentrations up to 1000 μg/plate, and in a rat bone marrow cytogenicity assay at up to paralyzing doses. A positive response was observed in the mouse lymphoma assay under conditions (80 and 100 μg/ml, in the absence of metabolic activation) which killed over 80% of the treated cells; there was no mutagenicity at 60 μg/ml and lower, concentrations which killed up to half of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations (1200 μg/ml and higher) which also killed over 80% of the treated cells. Mutagenicity testing is intended to simulate chronic (years to lifetime) exposure in an effort to determine potential carcinogenicity. Thus, a single positive mutagenicity response for a drug used infrequently and/or briefly is of questionable clinical relevance.

**Pregnancy: *Teratogenic Effects:*** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase.

Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in children below the age of 2 years have not been established.

**ADVERSE REACTIONS:** Tracrium produced few adverse reactions during extensive clinical trials, most of which were suggestive of histamine release (see PRECAUTIONS section). The overall incidence of clinically important adverse reactions was 7/875 or 0.8%.

Approximately one million patients received Tracrium during the first year following introduction to the U.S. market in December, 1983. Spontaneously reported adverse reactions were uncommon (approximately 0.02%). The following adverse reactions are among those most frequently reported, but there are insufficient data to support an estimate of their incidence:

**Musculoskeletal:** Inadequate block, prolonged block
**Cardiovascular:** Hypotension, vasodilatation (flushing), tachycardia, bradycardia
**Respiratory:** Dyspnea, bronchospasm, laryngospasm
**Integumentary:** Rash, urticaria, reaction at injection site

**DOSAGE AND ADMINISTRATION:** Tracrium should be administered intravenously. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION.

A Tracrium dose of 0.4 to 0.5 mg/kg, given as an intravenous bolus injection, is the recommended initial dose for most patients. With this dose, good or excellent conditions for nonemergency intubation can be expected in 2 to 2.5 minutes in most patients, with maximum neuromuscular blockade achieved approximately 3 to 5 minutes after injection. Clinically acceptable neuromuscular blockade under balanced anesthesia generally lasts 20 to 35 minutes; recovery to 25% of control is achieved approximately 35 to 45 minutes after injection, and recovery is usually 95% complete approximately 60 minutes after injection.

An initial Tracrium dose of 0.3 to 0.4 mg/kg is recommended following the use of succinylcholine for intubation under balanced anesthesia.

Tracrium is potentiated by isoflurane or enflurane anesthesia. The same initial Tracrium dose of 0.4 to 0.5 mg/kg may be used for intubation prior to administration of these inhalation agents; however, if Tracrium is first administered under steady state of isoflurane or enflurane, the initial Tracrium dose should be reduced by approximately one-third, i.e., to 0.25 to 0.35 mg/kg; with halothane, which has only a marginal (approximately 20%) potentiating effect on Tracrium, smaller dosage reductions may be considered.

Tracrium doses of 0.08 to 0.10 mg/kg are recommended for maintenance of neuromuscular blockade during prolonged surgical procedures. The first maintenance dose will generally be required 20 to 45 minutes after the initial Tracrium injection, but the need for maintenance doses should be determined by clinical criteria. Maintenance doses may be administered at relatively regular intervals for each patient, ranging approximately from 15 to 25 minutes under balanced anesthesia, slightly longer under isoflurane or enflurane.

An initial Tracrium dose of 0.3 to 0.4 mg/kg, given slowly or in divided doses over one minute, is recommended for patients with significant cardiovascular disease and for patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release.

Dosage reductions must be considered also in patients with neuromuscular disease, severe electrolyte disorders, or carcinomatosis in which potentiation of neuromuscular blockade or difficulties with reversal have been demonstrated.

No Tracrium dosage adjustments are required for patients with renal disease or for pediatric patients two years of age or older. In pediatric patients, maintenance doses may be required with slightly greater frequency than in adults.

**HOW SUPPLIED:** Tracrium Injection, 10 mg atracurium besylate in each ml. Ampuls of 5 ml (50 mg atracurium besylate per ampul). Box of 10 ampuls (NDC-0081-0940-10).

10 ml Multiple Dose Vial (100 mg atracurium besylate per vial). The multiple dose vial contains 0.9% benzyl alcohol added as a preservative. Box of 10 (NDC-0081-0940-95).

Store under refrigeration at 2° to 8°C (36° to 46°F); DO NOT FREEZE.

U.S. Patent No. 4179507 Printed in U.S.A.

**TRACRIUM® INJECTION**
*(atracurium besylate)*

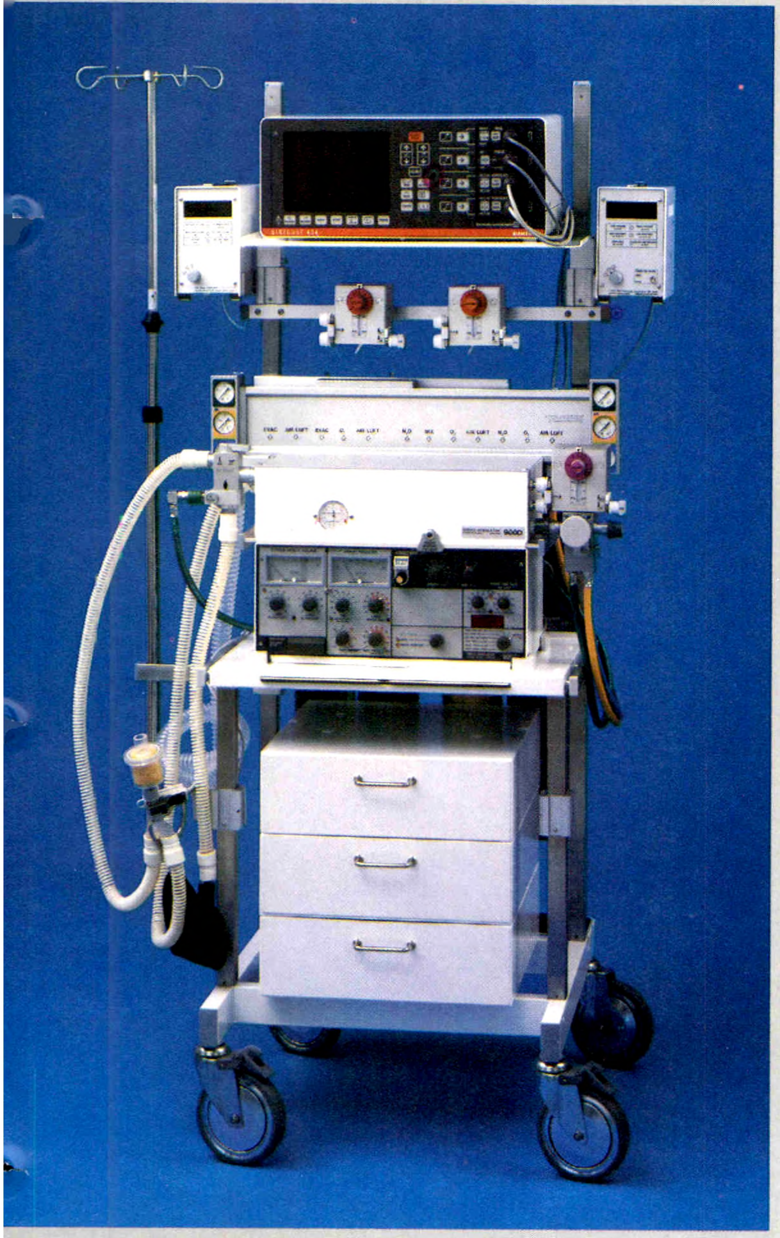
Wellcome
Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

84TRA8E

**SIEMENS**

Introducing the Servo Anesthesia System

# The advanced anesthesia system for pediatric and adult patients.



Now there's one highly versatile anesthesia system designed for routine and critical care cases involving pediatric as well as adult patients. It's the new Servo Anesthesia System from Siemens. Compact and modular in design, the system is human-engineered for ease of operation and highly accurate control...plus maximum safety.

## New versatility and efficiency in the OR

The system utilizes our Servo Ventilator, offering the most advanced technology available for both volume-controlled and pressure-supported anesthesia applications. A new ventilation mode, pressure support, enables patients to breathe spontaneously with the assistance of a pre-determined pressure. The system continuously monitors all important functions and provides instantaneous readings and audible/visual alarms.

## Advanced monitoring interface

The Servo Anesthesia System interfaces with a broad range of exclusive, innovative monitoring systems, including the $CO_2$ Analyzer 930, the Lung Mechanics Calculator 940 and the Sirecust 404.

## New ease of maintenance

You're assured of quality performance with a minimum of maintenance. The system requires only minimal servicing; the costs are extraordinarily low. And best of all, most maintenance is easily performed right on site by members of your own staff. No costly off-site service!

And you're further assured of immediate professional assistance, if necessary, from your Siemens sales and service representatives. It's all part of the Siemens commitment to superior products and systems for healthcare professionals and their patients.

For further information, contact
Siemens-Elema Ventilator Systems,
2360 No. Palmer Dr., Schaumburg,
Illinois 60195—(312) 397-5975, or
call toll-free 1-800-323-1281.

**Siemens...a pioneer in innovative healthcare systems.**

Siemens-Elema Ventilator Systems,
2360 No. Palmer Dr., Schaumburg, IL 60195
☐ Please send me information on Servo Anesthesia System.

Name
Institution
Address
City
State
Zip

MG/5820-009 WLM 174

## 24th CLINICAL CONFERENCE IN PEDIATRIC ANESTHESIOLOGY

### JANUARY 24, 25, & 26, 1986

To Be Held At The:

Los Angeles Marriott Hotel

For Information Write To:

**Wayne Herbert, M.D.
Program Director
Pediatric Anesthesiology
Foundation
Childrens Hospital of
Los Angeles
P.O. Box 54700
Los Angeles, CA 90054**

---

## Learn all YOU need to know about EEG monitoring and interpretation techniques.

**EEG MONITORING
IN ANESTHESIA
AND CRITICAL CARE
State of the Art: 1986**

**Betty L. Grundy, M.D. Course Director**

**March 14-16, 1986
Caesars Palace
Las Vegas, Nevada**

**Immediately precedes the annual meeting of
the International Anesthesia Research Society**

A distinguished faculty will outline the indications for EEG monitoring and present the state of the art in monitoring techniques and interpretation. Participants will be introduced to most of the commercially available EEG monitoring instruments in small group sessions, and will compare several EEG processing devices with traditional strip-chart EEGs simultaneously recorded in volunteer subjects.

Physicians completing this course will have the information needed to decide if, when, and how the EEG should be monitored in their operating room and critical care unit.

FACULTY:

Fred Bauman, R. Eeg T.
Warren Levy, M.D.
Judy Mackey-Hargadine, M.D.
John T. Martin, M.D.
Ira J. Rampil, M.D.
Lawrence S. Saidman, M.D.
James C. Scott, M.D.
Frank W. Sharbrough, M.D.
Stephen Slogoff, M.D.

Course Tuition:
$300.00 for all registrants before February 14, 1986; $350.00 afterwards. Enrollment is limited. Cancellation of registration by written notification only prior to February 21, 1986. There is a $40.00 cancellation fee.

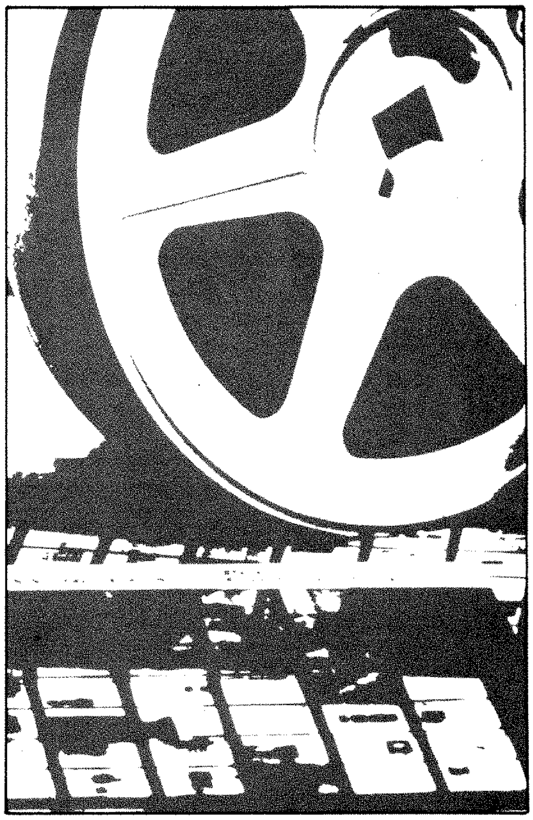
Send check payable to the Anesthesiology Alumni Association of Florida, Inc., in care of:

Mrs. Carolyn Schoenau
Executive Secretary
P.O. Box 13417
Gainesville, FL 32604
(904) 392-4616

**AMA Physician's Recognition Award--Credit 17 hours
Sponsored by the Anesthesiology Alumni Association of Florida, Inc.
Co-sponsored by the International Anesthesia Research Society**

---

## This Publication is available in Microform.



## University Microfilms International

Please send additional information

for ______________________
(name of publication)

Name______________________

Institution______________________

Street______________________

City______________________

State______________ Zip______________

300 North Zeeb Road
Dept. P.R.
Ann Arbor, Mi. 48106

# Classified Advertising

**ANESTHESIOLOGY FELLOW**

Two openings for a 6-month obstetrical anesthesia fellowship, one beginning October 1986 and the other, January 1987. Program includes a total of 6 months in the Departments of Anesthesiology at UCI Medical Center and Memorial Hospital Medical Center, Long Beach. Both are Level 3 Perinatal Centers with 4000 deliveries per year. There is opportunity to take part in clinical research and teaching of medical students. Applicants must be eligible for California state licensure. Inquiries from all qualified applicants are welcome. Contact Ho Joon Choi, MD, Director of Obstetric Anesthesia, University of California, Irvine Medical Center, 81A, Orange, CA 92668.

**ANESTHESIOLOGISTS**

BC/BE to join progressive group of MDs and CRNAs encompassing all specialties in attractive Gulf Coast community. Excellent quality of life, friendly city with four-year colleges and abundant opportunities for sailing, fishing, water sports, and hunting. Candidates must be well-trained, enthusiastic, and personable. Experienced anesthesiologists and/or recent graduates are encouraged to apply. Please send CV with reply to Box K22, % *Anesthesia & Analgesia*, Desk Editorial, 52 Vanderbilt Avenue, New York, New York 10017.

**PEDIATRIC ANESTHESIOLOGIST**

Seeking BC/BE pediatric anesthesiologist with fellowship training in pediatric anesthesia and intensive care. Duties will include resident instruction and operating room supervision. May include intensive care staffing for qualified individuals. Training and experience in pediatric cardiac, scoliosis, and craniofacial anesthesia desirable. New 220-bed children's hospital within the Washington University Medical Center, with a rapidly expanding surgical load. Opportunities available for clinical research and collaborative basic science investigation. Please send CV and references to John E. Forestner, MD, Director of Anesthesiology/Critical Care, St. Louis Children's Hospital, PO Box 14871, St. Louis, MO 63178. We are an equal opportunity/affirmative action employer.

**TUTORING FOR WRITTEN AND ORAL BOARD EXAMS:**

Individual or small group sessions given in New York City, San Francisco, and Hawaii. Unique approach to development of test-taking skills, including mock orals. Basic science emphasis. Include phone number in response. Reply to Box K23, % *Anesthesia and Analgesia*, Desk Editorial, 52 Vanderbilt Avenue, New York, NY 10017.

**NEUROANESTHESIOLOGIST**

The Department of Anesthesiology/CCM at the University Health Center of Pittsburgh seeks a director of neuroanesthesia. Role includes excellent potential for clinical and basic research and collaboration with creative and sane neurosurgeons. Applicants must be board certified and have consequential neuroanesthesia experience. An equal opportunity/affirmative action employer. Send credentials to Peter M. Winter, MD, University Health Center of Pittsburgh, 1385 Scaife Hall, Pittsburgh, PA 15261 (412) 624-2955.

**SOUTHWESTERN PA ANESTHESIOLOGIST**

BE/BC to join group. All types of surgery except open heart. Opening immediately. Excellent compensation and future for right person. Response confidential. Pittsburgh area. Submit CV to Box L26, % *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

**THE DEPARTMENT OF ANESTHESIOLOGY, ORAL ROBERTS UNIVERSITY SCHOOL OF MEDICINE**

currently has openings for Assistant/Associate Professor with interests in teaching, clinical practice and research. Excellent opportunity for board eligible/board certified physician in an institution dedicated to philosophy of Whole Person Medicine. Rank and salary commensurate with qualifications and negotiable. The City of Faith Medical and Research Center is a Christian ministry that employs without regard to race, color, sex, age, handicap, national origin or status as a veteran. Send CV and names of three references to James Mayhew, MD, Chairman, Department of Anesthesiology, Oral Roberts University School of Medicine, City of Faith Medical & Research Center, 8181 South Lewis, Tulsa, OK 74137-1270.

**"ANESTHESIA, YOUR BABY, AND YOU"**

This obstetric anesthesia VIDEOTAPE can help you with patient education and informed consent, as well as nursing and student education. Contact: APPCOR PRODUCTIONS, 3652 Carleton St, San Diego, CA 92106.

**ANESTHESIOLOGIST—PHOENIX, ARIZONA AREA**

JCAH Hospital Accreditation—no obstetrics. Board certification highly desirable. Unique group practice offers very early partnership. Available now! Send CV to Box K24, % *Anesthesia and Analgesia*, Desk Editorial, 52 Vanderbilt Avenue, New York, NY 10017.

**ANESTHESIOLOGIST**

Head of the Department of Pediatric Anesthesiology, The Children's Hospital of Buffalo, University at Buffalo, State University of New York. We are seeking a person who is able to give professional and administrative leadership of highest quality to a department with programs of patient care, teaching, and research. Board certified anesthesiologist with special training in pediatric anesthesiology. Send curriculum vitae and bibliography to Donald R. Cooney, MD, Department of Pediatric Surgery, The Children's Hospital of Buffalo, 219 Bryant Street, Buffalo, NY 14222. An equal opportunity/affirmative action employer.

**PRIVATE TUTORING AVAILABLE FOR WRITTEN AND ORAL BOARD EXAMS**

Send name, address, and phone to Box ANA 5-84-E, % *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Co., Inc., 52 Vanderbilt Avenue, New York, NY 10017.

**NORTH CAROLINA**

Temporary and permanent BE/BC anesthesiologists needed to join fee-for-service group in small community in heart of Blue Ridge Mountains. Salary first year. Send inquiries and CV to Watauga Anesthesia Associates, PA, 301 Birch Street, Boone, NC 28607.

**ANESTHESIOLOGY RESIDENT**

Currently accepting applications for PGY-3 anesthesiology resident to begin 1/86. Send CV to J. H. Eisele Jr, MD, Chairman, Anesthesiology, UC Davis Medical Center, 2315 Stockton Boulevard, Sacramento, CA 95817. An affirmative action/equal opportunity employer.

## CLASSIFIED ADS

*Anesthesia and Analgesia* makes available classified advertising space for those interested in obtaining positions, or wishing to announce meetings, postgraduate courses, or other events. Display space (minimum ¼ page) is also available through Pharmaceutical Media, Inc. Rates for classified advertising: $.90 per word, minimum twenty words; or $1.00 per word for box number ads. Copy deadline 7 weeks prior to publication, e.g., for the March issue, copy should be received by the 1st of January. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. Ad copy, subject to acceptance by publisher, should be mailed to:

*Anesthesia and Analgesia*
Desk Editorial
Classified Ads
Elsevier Science Publishing Co, Inc,
52 Vanderbilt Avenue, New York, NY 10017.

Make checks payable to Elsevier Science Publishing Co, Inc.

**ANESTHESIOLOGIST**

Diplomate American Board of Anesthesiology, American medical graduate, diplomate National Board of Medical Examiners. Seven years experience including academic/university/private practice, to provide anesthesia for all surgical procedures. Seek solo/group/partnership arrangement. Fee-for-service or salary. Western United States preferred, other areas considered. California license. Excellent references. Reply Box 3723, Walnut Creek, CA 94598.

**FREELANCE ANESTHETISTS**

Temporary & Permanent—Medical Anesthesiologists—CRNAs. Home-based throughout US. If you need an anesthetist call 1-800-521-6750, ALL-STATES MEDICAL PLACEMENT AGENCY, Box 91, LaSalle, MI 48145 or 313-241-1418 (MI).

**ROCKY MTS./SOUTHWEST**

We have career and temporary positions available from solo to large group practice in the Rocky Mts. and Southwest. Expenses paid; partnerships usually available. Please contact Southwest Anesthesia Services, R.R. #9 Box 96 MM, Santa Fe, NM 87501. (505) 983-7371.

**ANESTHESIOLOGIST**

AMG, BE, passed part I ABA, completing cardiac fellowship June 1986. Seeking practice in Southeastern city. Reply to Box L27, ℅ *Anesthesia & Analgesia*, Desk Editorial, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

**ANESTHESIOLOGIST**

Full-time faculty position at Assistant/Associate level in young department with emphasis on teaching and research. Complete clinical services in one hospital. Prerequisites: fellowship year or equivalent training in subspecialty area; board eligibility; meet California license requirements; ability to write scholarly articles; and a genuine commitment to inquiry. Send curriculum vitae and *names of three references* to John H. Eisele Jr, MD, Anesthesiology Department, University of California, Davis, Medical Center, 2315 Stockton Boulevard, Sacramento, CA 95817. Position open until filled but not later than February 28, 1986. We are an Equal Opportunity/Affirmative Action Employer.

**POSITION WANTED**

Anesthesiologist, BE, AMG, orals in 1986, excellent training, proficient in all phases of anesthesia practice. Seeking relocation with progressive group, any area. Reply to Box L28, ℅ *Anesthesia and Analgesia*, Desk Editorial, 52 Vanderbilt Avenue, New York, NY 10017.

**GEORGIA**

Fourth year postgraduate positions available in the Department of Anesthesiology at the Medical College of Georgia in Augusta, GA. These positions reflect the Department's interest in the developing clinician scientist in neurosurgical, cardiothoracic, obstetric, and pediatric anesthesia and pain management. Education and career development are priorities. EOE/AAP. J-3243. Contact Dan C. Martin, MD, Department of Anesthesiology, Medical College of Georgia, Augusta, GA 30912.

**WORLDWIDE ANESTHESIA**

is an exciting organization of anesthesiologists and CRNAs who specialize in relief services and provide qualified candidates for permanent positions throughout the US. To be included in our computerized data base or to recruit from the nation's largest resources of anesthesia personnel, call or write Worldwide Anesthesia, Box 1547, Ukiah, CA 95482. Nationwide 1-800-327-8427. "Over a decade of placement experience."

**PERMANENT POSITION WANTED**

CRNA—experienced, wishes busy situation, solo or group, best of remuneration. 1-800-521-6750.

**ANESTHESIOLOGIST**

Board certified anesthesiologist, 3–5 years experience for busy Midwest practice in 700-bed hospital. Send CV to Box H19, ℅ *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

**ANESTHESIOLOGIST**

Southern California Management Corporation has opportunities—both entry and practice/management—for board eligible or certified anesthesiologists to serve hospitals under contract. Attractive income, benefits, and profit-sharing package. Reply to box L29, ℅ *Anesthesia and Analgesia*, Desk Editorial, Elsevier Science Publishing Company, 52 Vanderbilt Avenue, New York, NY 10017.

**UNIVERSITY OF MIAMI COMPREHENSIVE REVIEW COURSE IN ANESTHESIOLOGY MAY 6–11, 1986**

Will be held at the James L. Knight Convention Center/Hyatt Regency, Miami, Florida. For more information contact Professional Seminars, PO Box 021318, Miami, FL 33101. Telephone 305-547-6411.

**RHODE ISLAND: CHIEF ANESTHESIOLOGIST**

Full time board-certified or board-eligible anesthesiologist needed to supervise anesthesia program in the VA Medical Center, Providence, RI. This is a 329-bed general hospital with an active surgical program. This medical center is fully affiliated with the Program in Medicine of Brown University. Providence is an attractive New England city only an hour from Boston and in close proximity to the famed resort area of Newport. Recreational opportunities abound here in the "Ocean State." Send CV and three references to Benjamin T. Jackson, MD, Chief, Surgical Service (112), VA Medical Center, Davis Park, Providence, RI 02908. AN EQUAL OPPORTUNITY EMPLOYER.

**POSITION WANTED**
**BE ANESTHESIOLOGIST**

Three years experience. NY and FL licenses. Available for immediate relocation. All offers considered. Reply to Box K25, ℅ *Anesthesia and Analgesia*, Desk Editorial, 52 Vanderbilt Avenue, New York, NY 10017.

**ANESTHESIOLOGISTS**

Excellent, prequalified individuals available to join your group on a career or temporary basis. For more information please contact: Southwest Anesthesia Services, PO Box 5719, Santa Fe, New Mexico 87502, (505) 983-7371.

**MDAS OR CRNAS: TRANS-AMERICAN ANESTHETISTS, WEST**

Temporary or Permanent MDAs, CRNAs, ready to serve you, up-to-date skills, cooperative, licensed, insured professionals caring about you. Call 1-800-762-1258, Box 24432, Colorado Springs, CO 80918, or 303-598-2788 (CO).

**FLORIDA**

Tampa Bay area. Anesthesiologist to join multispecialty group. Fee-for-service with first year guarantee. Reply with CV to Brandon Surgical Group, 710 Oakfield Drive, Brandon, FL 33511.

**CALIFORNIA: ANESTHESIOLOGIST**

Full-time faculty position at Associate/Full Professor level in young department with emphasis on teaching and research. Complete clinical services in one hospital. Prerequisites include board certified; meet California license requirements; clinical expertise in neuro, pain and/or pediatrics; demonstrated ability as a research scientist; and ability to write scholarly articles. Send curriculum vitae, bibliography and *names of five references* to John H. Eisele Jr, MD, Anesthesiology Department, University of California, Davis, Medical Center, 2315 Stockton Boulevard, Sacramento, CA 95817. Position open until filled but not later than February 28, 1986. We are an Equal Opportunity/Affirmative Action Employer.

## ANESTHESIOLOGISTS

**St. Vincent Medical Center's Anesthesia Department** is expanding. We are seeking 2 board certified or board eligible anesthesiologists to join an 8 member BC/BE group with 15 CRNA's.

You will need 3 to 5 years experience with all types of anesthesia and intra-operative monitoring techniques.

**St. Vincent** is a 741-bed community teaching hospital with full surgical facilities, including neurological, open heart, retinal, vascular, obstetrical, plastic, as well as ambulatory outpatient surgery.

Located in one of Ohio's newest cities, Toledo boasts of spectacular waterfront developments, an art museum, symphony, theater and zoo rated among the top ten in the country, fine restaurants and shopping centers. In addition, year-round sports facilities are available along with spectator sports such as baseball and hockey.

For immediate consideration, please send your C.V. and a cover letter to: **Lynn Scott, Manager Recruitment Employment,**

St. Vincent Medical Center
**2213 Cherry St. • Toledo, OH 43608**
An Equal Opportunity Employer

---

## CALIFORNIA

Kern Medical Center, a UCLA affiliated teaching hospital located in Bakersfield, 105 miles north of Los Angeles, is recruiting a chairperson. Candidates must be Board Certified; have 5 years clinical experience; have experience in organized medical staff departmental tasks; and be qualified for an appropriate academic appointment.

KMC has 240 beds hospital; 16,000 annual admissions; 100,000 outpatient and 60,000 emergency visits; 3,600 obstetrical deliveries; and 5,000 surgical cases in a variety of specialties including trauma.

There is a competitive compensation package incorporating base salary, practice plan financial incentive, and outstanding benefits.

Send letter of inquiry with Curriculum Vitae to:

**Donald A. Lackey, M.D.**
**Medical Director**
**Chairman, Search Committee**
**Kern Medical Center**
**1830 Flower Street**
**Bakersfield, California 93305**

EO/AA Employer

---

## ANESTHESIA STAFFING CRISIS

CALL 1-800 FAST GAS (327-8427)
24 HOUR HOT LINE

WORLDWIDE ANESTHESIA ASSOCIATES, INC.

THE NATION'S LARGEST PROVIDER OF PROFESSIONAL ANESTHESIA PERSONNEL

ANESTHESIOLOGISTS • CERTIFIED REGISTERED NURSE ANESTHETISTS • EMERGENCY AND SCHEDULED RELIEF • LOCUM TENENS • CONTRACT MANAGEMENT • PERMANENT RECRUITING •

Worldwide Anesthesia Associates, Inc.

P.O. Box 1547 • UKIAH, CALIFORNIA 95482 • U.S.A.

---

## ANESTHESIOLOGIST

Board Certified/Eligible Anesthesiologist needed as Associate in Section of Anesthesia of 110 member Multi-specialty Clinic which serves as a referral center for surrounding areas of Northeastern Pennsylvania and the Southern Tier of New York State.

State of the art facility. Medical school teaching affiliation through surgical residency program provides a stimulating environment. Tertiary Care Center performing 6500 anesthetic procedures per year. Most types of surgery performed with emphasis on cardiovascular and neurosurgery.

Area provides attractive living conditions with many summer and winter recreational activities readily available. Easy access to major metropolitan areas. Excellent salary and fringe benefits. Respond with Curriculum Vitae to:

**G. V. Ippolito**
**Assistant Vice President**
**GUTHRIE CLINIC**
**Sayre, PA 18840**
**(717) 888-5858**

# Soothing news for busy anesthesiologists

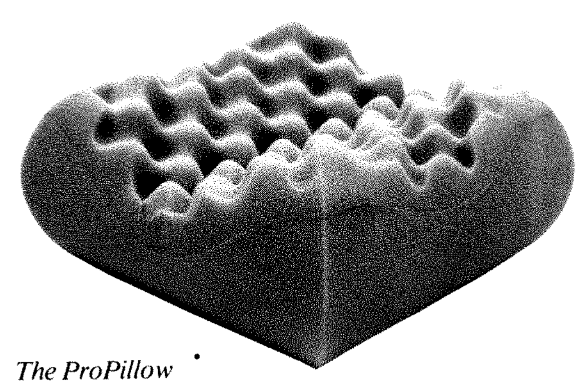
Dr. Smith was having another busy day in surgery. One Swan-Ganz placement had been unusually time-consuming. Plus the patient had been difficult to intubate. To top it off, the pump time had been excessive.

Down the hall, Dr. Jones had a marathon case involving a young woman undergoing a tuboplasty for infertility. Finally, 5½ hours later the surgeons were closing the skin. He heaved a sigh of relief and automatically leveled the table from the previous several hours where the Trendelenberg position had been necessary.

But these two stories don't end here. About 28 days later, *both patients had a bald spot about the size of a silver dollar at the occiput... exactly where their heads were resting on the table for hours on end.* They were each advised by their surgeons that they had a 50% chance of their hair growing back within the next year. But there was an equal chance that their hair wouldn't grow back at all. The anesthesiologists on both cases were never told of the problem.

## The ProPillow takes the pressure off

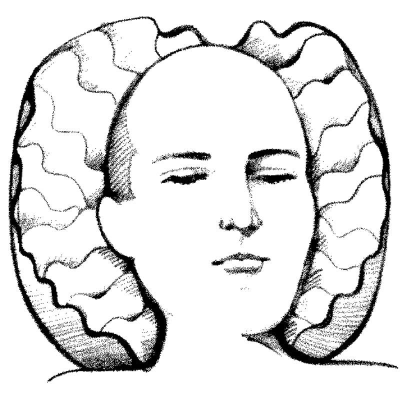
The ProPillow Anesthesia Pillow helps "take off the pressure" to the circulation of the face and scalp during prolonged anesthesia. It's unique "hills and valleys" construction creates a protective effect by evenly distributing the weight of the head and neck. Result: no more pressure in one area greater than any other area. And those precipitous swings in blood pressure are less likely to result in ischemia to the scalp. All this lessens the chance of post-op alopecia.



*The ProPillow Anesthesia Pillow*

## The end of the juggling act

The ProPillow lets you off gracefully from attempts to juggle the heavy head (10 lbs.) during intubation. The ProPillow Anesthesia Pillow stabilizes (by gently gripping) the patient's head in the neutral, "sniffing", position. It even helps free up one of your hands when you're using a mask for short cases.



*The ProPillow Anesthesia Pillow stabilizes the head, supports the neck and helps take the pressure off.*

## An eye for details

Awake patients really appreciate the comfort of the ProPillow Anesthesia Pillow. Especially the eye patients who are undergoing removal of cataracts with intra-ocular lens implants. And the ProPillow fits inside the frame used by Opthalmologists during this tedious microsurgery. Less squirming... and possibly sedation required.

## And the price is right

Because of the ProPillow's reasonable price, some say we should call it disposable. But it is made to last for up to 50 cases. You can use a nurse's bouffant cap to cover the ProPillow. Or even spot wash and air-dry it. It's made from a bright blue, breathable, resilient polyurethane foam that's 100% non-allergenic and non-irritating to skin.

It's easy to order the ProPillow Anesthesia Pillow! Call us **TOLL FREE** at **(800) 227-0517 outside California,** or **(800) 554-5541 inside California.** Or, give this page to your head nurse or purchasing agent to get the ProPillow promptly. We ship within 24 hours. *Pediatric Size available, ask for details.

**ProTechPacific**
**1221 Andersen Drive**
**San Rafael, CA 94901**

Makers of the **ProPillow Anesthesia Pillow, NECK-PIL-O Neck Support Pillow, DIXSEY Hip Abduction pillow** and the new **STRAPEZE * Velcro Endotracheal Tube stabilizer.**

# IARS MEMBERSHIP

## FOR YOUR IN-TRAINING AND CONTINUING MEDICAL EDUCATION

The International Anesthesia Research Society is a non-profit, scientific and educational corporation of the State of Ohio, founded in 1922 "to foster progress and research in anesthesia." To this end the Society

Publishes the oldest journal in the specialty, *Anesthesia and Analgesia*

Sponsors an annual scientific meeting (Congress) which is held in March each year

Funds anesthesia-related research through the IARS B.B. Sankey Anesthesia Advancement Award

Membership in the IARS is voluntary; it is also separate and distinct from membership in any other local, state, regional or national anesthesia organization or association. Membership is open to individuals who qualify in the various categories shown below; who complete the appropriate application and submit it to the IARS Cleveland office with the applicable dues. All memberships include a subscription to *Anesthesia and Analgesia*. Members and Associate Members are entitled to a reduced registration fee at the IARS annual meeting; Educational Members pay no registration fee.

## . . . . MEMBERSHIP CATEGORIES . . . .

**MEMBERSHIP:** Open to individuals with doctorate degrees, who are licensed to practice in the medical, osteopathic, dental or veterinary medicine fields (i.e., MD, MB, DO, DDS, DMD, DVM); and to individuals with doctorate degrees in any scientific discipline (PhD), who are engaged in academic, private or commercial research.

**ASSOCIATE MEMBERSHIP:** Open to individuals in the allied health professions, duly certified by their professional accrediting organization as nurse anesthetists (CRNA); respiratory therapists or technicians (RRT or CRTT); physician/anesthesia assistants (PA/MMS); and other allied health professionals in anesthesia-related practice.

*Annual Dues for Members and Associate Members:* $50.00 U.S.; $61.00 foreign. These memberships are entered on a calendar year basis only.

**EDUCATIONAL MEMBERSHIP:** Open (with certification by program director) to doctors (interns/residents) enrolled in anesthesiology training programs; nurses enrolled in nurse anesthesia schools; students enrolled in programs leading to certification as physician assistants, respiratory therapists or technicians

*Annual Dues for Educational Members:* One-half of member rate. These memberships are entered in January or July for 2, 3, or 4 year periods. Applications, certified by program directors, must accompany check to cover full membership period.

---

International Anesthesia Research Society
3645 Warrensville Center Road, Cleveland, Ohio 44122, USA

Please send me ________ application(s) for: Membership (______)
Associate Membership (______)
Educational Membership (______)

Please print clearly: ______________________________
Name and Degree (MD, DO, CRNA, RN, RRT, etc.)

______________________________
Street Address　　City, State, Zip Code (country)

# INDEX TO ADVERTISERS

- American Critical Care
  - *Hespan* . . . . . . . . A16, A17, A18
- American Pharmaseal
  - *CTL* . . . . . . . . Cover 3
- Anaquest
  - *Forane* . . . . . . . . A9 thru A12
- Anesthesiology Alumni Associates of Florida
  - *Continuing Education* . . . . . . . . A28
- Breon Laboratories
  - *Marcaine* . . . . . . . . A19, A20
- Bristol Laboratories
  - *Stadol* . . . . . . . . Cover 4
- Burroughs Wellcome Co.
  - *Tracrium* . . . . . . . . A2
  - *Tracrium* . . . . . . . . A23 thru A26
- Classified Advertising . . . . . . . . A29, A30
- CNS, Inc.
  - *Monitors* . . . . . . . . A13
- Guthrie Clinic Ltd.
  - *Employment Opportunities* . . . . . . . . A31
- Halocarbon Laboratories
  - *Halothane* . . . . . . . . A1
- Kern Medical Center
  - *Employment Opportunities* . . . . . . . . A31
- Ohmeda
  - *Biox 3700* . . . . . . . . A21
- Organon Pharmaceuticals
  - *Regonal* . . . . . . . . Cover 2, A1
- Pediatric Anesthesiology Foundation
  - *Continuing Education* . . . . . . . . A28
- ProTechPacific
  - *ProPillow* . . . . . . . . A32
  - *Strapeze* . . . . . . . . A22
- Puritan-Bennett Corp.
  - *Institutional* . . . . . . . . A7
- St. Vincent Medical Center
  - *Employment Opportunities* . . . . . . . . A31
- Siemens Corporation
  - *Servo Anesthesia System* . . . . . . . . A27
- Siemens Elema
  - *Ventilator* . . . . . . . . A14, A15
- Worldwide Anesthesia Associates
  - *Employment Opportunities* . . . . . . . . A31

*Advertising Office*: Pharmaceutical Media, Inc., 130 Madison Avenue, 6th Floor, New York 10016. Telephone: (212) 685-5010

# CHOICE

**Introducing**
**the Pharmaseal® Custom Catheter**
**Insertion Tray Program**

No two patients, no two physicians, no two procedures are alike. Why should two trays be?

We understand your need for versatility of product selection, and in response, we've designed our new *Custom* Catheter Insertion Tray Program. Now, you have a choice.

You can create your own trays from our full line of components. And once we receive your order, we'll deliver your custom trays in just 45 days. That's uncustomarily fast.

Working closely with your Pharmaseal representative, you can design the ideal trays for your pulmonary artery and central vein catheterization procedures.

Choose from over 165 high quality components, including a wide range of catheters and catheter components. Select local anesthetic, prepping and guiding components, and much more.

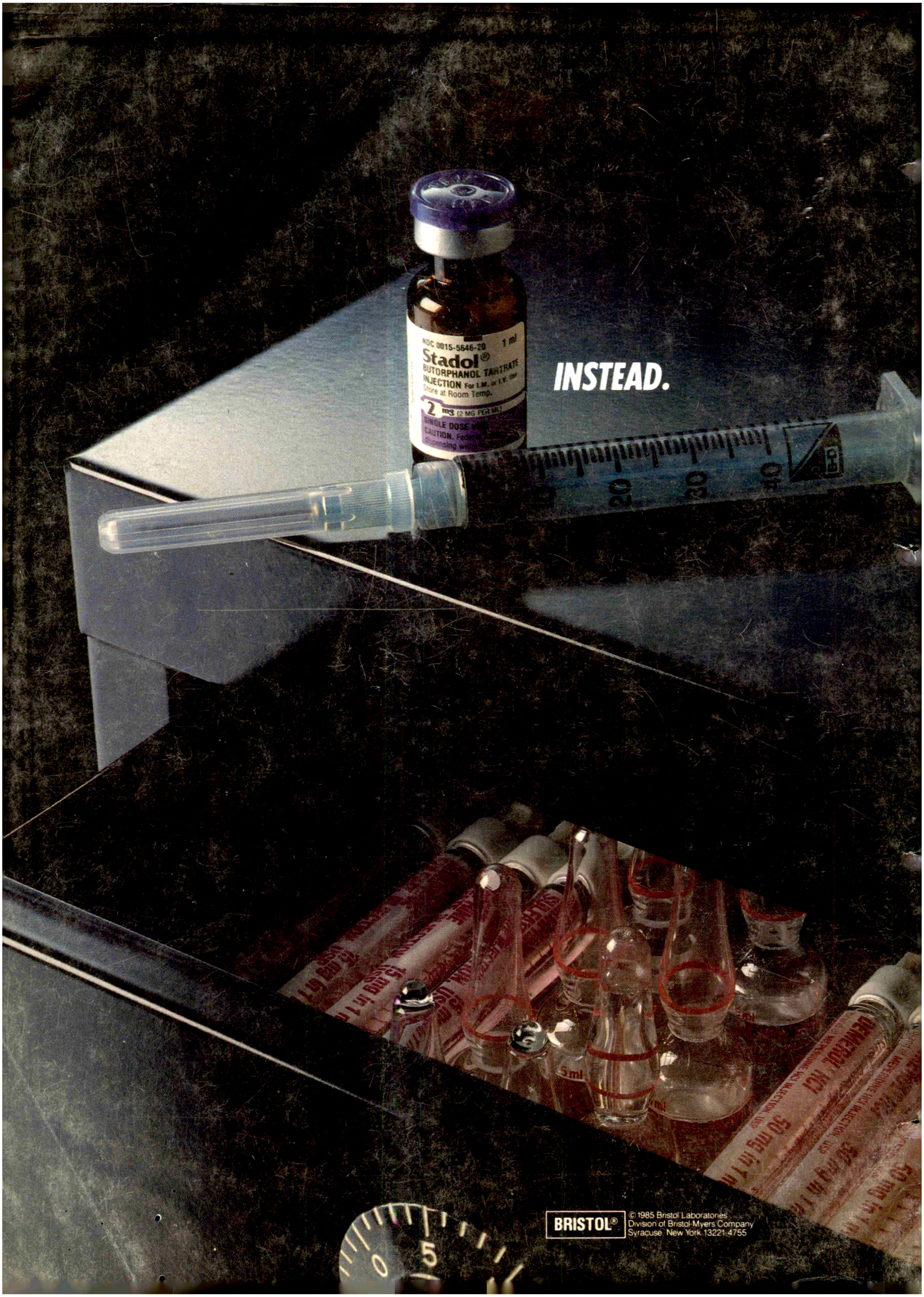
The Pharmaseal Custom Catheter Insertion Tray Program. Make it your first choice for all your needs.

For more information, contact American Pharmaseal Company, P.O. Box 5900, Valencia, CA 91355-8900. Or call toll-free 1-800-242-3549.

**American Pharmaseal Company**

American Hospital Supply Corporation

©American Hospital Supply Corporation



BRISTOL®
© 1985 Bristol Laboratories
Division of Bristol-Myers Company
Syracuse, New York 13221-4755

Ten-Year Cumulative Index 1975–1984

Acc.
9.12.86

# Anesthesia and Analgesia

**Journal of the International Anesthesia Research Society**
Oldest Publication in the Specialty—Established 1922

ORGANON PHARMACEUTICALS

Organon

A Division of ORGANON Inc., West Orange, NJ 07052
(201) 325-4500 Telex 138 201

June 1985

Dear Colleague:

Since the introduction of Pavulon® (pancuronium bromide) over 12 years ago, Organon Pharmaceuticals has been dedicated to serving the needs of the anesthesia community. This dedication was again in evidence when we added Regonol® (pyridostigmine bromide) to your armamentarium.

In 1984, Organon's research activity resulted in the newest, most advanced agent in its class, Norcuron® (vecuronium bromide). Norcuron, like its predecessor Pavulon, represents the current state of the art.

Organon's commitment to anesthesia research will continue. Our dedication to serving the needs of the anesthesia community remains a top priority. That is why Organon is pleased to have had the opportunity to sponsor publication of this index.

Very truly yours,

Edward Miller

Edward Miller, M.D.
Director of Medical Services

Anesthesia
and Analgesia

# Ten-Year Cumulative Index
# 1975–1984

Journal of the International Anesthesia Research Society

# BOARD OF TRUSTEES
## International Anesthesia Research Society

Dean H. Morrow, MD, *Chairman*
Bruce F. Cullen, MD, *Vice Chairman*
Emerson A. Moffitt, MD, *Executive Secretary*
Douglas B. Craig, MD
E. Paul Didier, MD
Judith H. Donegan, MD, PhD
Noel W. Lawson, MD
John T. Martin, MD
Robert K. Stoelting, MD
John L. Waller, MD
Paul R. Dumke, MD, *Emeritus Trustee*
Kenneth K. Keown, MD, *Emeritus Trustee*
Morris T. Nicholson, MD, *Emeritus Trustee*
B. B. Sankey, MD, *Emeritus Trustee*
T. H. Seldon, MD, *Emeritus Trustee*

# EDITORIAL BOARD
## Anesthesia and Analgesia

*Editor in Chief*
Nicholas M. Greene, MD

*Editors*
Henrik H. Bendixen, MD
David R. Bevan, MA, MB, BChir
D. Ryan Cook, MD
Michael J. Cousins, MD, FFARACS, FFARCS
Benjamin G. Covino, MD
Norig Ellison, MD
Alison B. Froese, MD
Edward D. Miller, MD
Daniel M. Philbin, MD
Cedric Prys-Roberts, MA, DM, PhD
J. Gerald Reves, MD
John H. Tinker, MD
K. C. Wong, MD, PhD

*Book Review Editor*
Norig Ellison, MD

Anesthesia
and Analgesia

# Author Index

# Ten-Year Cumulative Index
## 1975–1984

Journal of the International Anesthesia Research Society.

# Author Index

Aasheim GM, see Pflug AE
Abajian JC, Mellish P, Browne AF, Perkins FM, Lambert DH, Mazuzan JE Jr. Spinal anesthesia for surgery in the high-risk infant 1984;63:359
Abboud CF, see Messick JM Jr
Abboud TK, Afrasiabi A, Sarkis F, Daftarian F, Nagappala S, Noueihed R, Kuhnert BR, Miller F. Continuous infusion epidural analgesia in parturients receiving bupivacaine, chloroprocaine, or lidocaine—maternal, fetal, and neonatal effects 1984;63:421
  An easy approach for difficult spinal anesthesia in the parturient (letter) 1981;60:770
  Curtis JP, Shnider SM, Earl S, Henriksen EH. Comparison of the effects of sodium citrate and Gelusil on gastric acidity and volume (abstract) 1982;61:167
  David S. Epidural anesthesia for elective cesarean section (letter) 1984;63:624
  David S, Nagappala S, Costandi J, Yanagi T, Haroutunian S, Yeh SU. Maternal, fetal, and neonatal effects of lidocaine with and without epinephrine for epidural anesthesia in obstetrics 1984;63:973
  Interpretation of negative results (letter) 1983;62:1045
  Khoo SS, Miller F, Doan T, Henriksen EH. Maternal, fetal, and neonatal responses after epidural anesthesia with bupivacaine, 2-chloroprocaine, or lidocaine 1982;61:638
  Kim KC, Noueihed R, Kuhnert BR, DerMardirossian N, Moumdjian J, Sarkis F, Nagappala S. Epidural bupivacaine, chloroprocaine, or lidocaine for cesarean section—maternal and neonatal effects 1983;62:914
  Raya J, Sadri S, Grobler N, Stine L, Miller F. Fetal and maternal cardiovascular effects of atropine and glycopyrrolate 1983;62:426
  Sarkis F, Blikian A, Varakian L, Earl S, Hendriksen E. Lack of adverse neonatal neurobehavioral effects of lidocaine 1983;62:473
  see Hughes SC
  see Rosen MA
  Shnider SM, Wright RG, Rolbin SH, Craft JB, Henriksen EH, Johnson J, Jones MJ, Hughes SC, Levinson G. Enflurane analgesia in obstetrics 1981;60:133
Abel EL. Marihuana (book review) 1981;60:367
Abel FL, McCutcheon EP. Cardiovascular function principles and application (book review) 1979;58:534
Abernethy DR, see Martyn JAJ
Abouleish E. Caudal analgesia for quadruplet delivery 1976;55:61
  de la Vega S, Blendinger I et al. Long-term follow-up of epidural blood patch 1975;54:459
  Depp R. Acupuncture in obstetrics 1975;54:83
  Pain control in obstetrics (book review) 1978;57:385
  Pan P. Placental transfer of hydroxyzine hydrochloride and its effect on the human neonate (abstract) 1984;63:176
  Postpartum hypertension and convulsion after oxytocic drugs 1976;55:813
  see Kang YG
  Spinal anesthesia after laminectomy (letter) 1981;60:169
  Taylor FH. Effect of morphine-diazepam on signs of anesthesia, and dreams of patients under $N_2O$ for cesarean section 1976;55:702
  Wadhwa RK, de la Vega S et al. Regional analgesia following epidural blood patch 1975;54:634
Abrahamson S, see Lee K
Abram A, see Epstein HM
Abram SE, Asiddao CB, Reynolds AC. Increased skin temperature during transcutaneous electrical stimulation 1980;59:22
  Intra-arterial reserpine (letter) 1980;59:889
  Reynolds AC, Cusick JF. Failure of naloxone to reverse analgesia from transcutaneous electrical stimulation in patients with chronic pain 1981;60:81
  see Maitra AM
  see Palmer SK
  Subarachnoid corticosteroid injection following inadequate response to epidural steroids for sciatica 1978;57:313
Abramawitz MD, see Brodsky JB
Abramowitz R, see Oliverio R Jr
Abrams LM, see Fyman PN
Abston PA, Priano LL. Bartter's syndrome: anesthetic implications based on pathophysiology and treatment 1981;60:764
  see Gloyna DF
Acinapura A, see Capan LM
Adair JC, Ring WH. Management of epiglottitis in children 1975;54:622
  see Ring WH
Adams AP, Hahn CEW. Principles and practice of blood-gas analysis (book review) 1980;59:165
Adams B, see Brock-Utne JG
Adams HJ, Blair MR Jr, Takman BH. The local anesthetic activity of tetrodotoxin alone and in combination with vasoconstrictors and local anesthetics 1976;55:568
Adams HR, Mathew BP, Teske RH et al. Neuromuscular blocking effects of aminoglycoside antibiotics on fast- and slow-contracting muscles of the cat 1976;55:500
Adams ML, see McKay RD
Adler E, see Youngberg JA
Afrasiabi A, see Abboud TK
Aggarwal S. Handbook of neuroanesthesia: clinical and physiological essentials (book review) 1984;63:1051
Agoston S, see Baraka A
Ahlquist RP. Adrenergic receptors and others; Fourteenth Annual Becton, Dickinson and Company Oscar Schwidetzky Memorial Lecture 1979;58:510
Ahmad I, see Sosis M
Ahnefeld FW, see Burri C
Aidinis SJ, see Marsh ML
Airola VM. Postoperative venous air embolism 1980;59:297
Aizenman B, see Sparks DL
Akkineni SR, see Ramamurthy S
  see Winnie AP
Akutagawa T, Kitahata LM, Saito H, Collins JG, Katz JD. Magnesium enhances local anesthetic nerve block of frog sciatic nerve 1984;63:111
Alban J, see Philbin DM
Albe-Fessard DG, see Bonica JJ
Albert CA, Kwan A, Kim C, Shibuya J, Albert SN. A waste gas scavenging valve for pediatric systems 1977;56:291
Albert SN, see Albert CA
  see Kwan AM
  Warming skin-preparation solutions (correspondence) 1977;56:748
Alberternst EA, see Blitt CD
Albin MS, Chang JL, Tung AS, Maivald P, Pautler S. Anesthesia for the sitting position (correspondence) 1977;56:325
  see Newfield P
  see Waterman PM
Albrecht RF, see Hoffman WE
  see Janeczko GF
  see Miletich DJ
  see Zahed B
Albrecht WH, see Ravindran RS
Albright G, see Samuels SI

Aldrete JA, Cubillos P. Phenytoin improves hemodynamic tolerance and survival after severe hypoxia 1984;63:1021
de Campo T, Usubiaga LE, Renck R, Suzuki D, Witt WO. Comparison of butorphanol and morphine as analgesics for coronary bypass surgery 1983;62:78
Lowe HJ, Virtue RW. Low flow and closed system anesthesia (book review) 1979;58:352
Phenytoin in the treatment of cerebral ischemia (letter) 1981;60:616
Romo-Salas F, Arora S, Wilson R, Rutherford R. Reverse arterial blood flow as a pathway for central nervous system toxic responses following injection of local anesthetics 1978;57:428
see Arguelles JE
see Carrow DJ
see Cullen JP
see Geevarghese KP
see Guerra F
see Nicholson JA
see Sampson JF
Tan ST, Carrow DJ et al. "Pentazepam" (pentazocine + diazepam) supplementing local analgesia for laparoscopic sterilization 1976;55:177
Virtue RW. Scavenging of anesthetic gases (letter) 1980;59:163
Aldrete JE, Stanley TH. Trends in intravenous anesthesia (book review) 1980;59:812
Aldrete JS, see Gelman S
Aleniewski MI, Bulas BJ, Maderazo L, Mendoza C. Intramuscular lorazepam versus pentobarbital premedication: a comparison of patient sedation, anxiolysis, and recall 1977;56:489
Alevizou FR, see Balamoutsos NG
Alexander GD, Crowley TP. Nebulizer contamination (correspondence) 1978;57:748
Skupski JN, Brown EM. The role of nitrous oxide in postoperative nausea and vomiting (abstract) 1984;63:175
Alexander JJ, Wall J. Righting the wrongs of writing: copy editors speak out (editor's choice) 1976;55:219
Alexander SC, see Atlee JL III
Alfery DD, Denlinger JK. Profound hypotension following a "test dose" of bretylium tosylate 1979;58:516
see Benumof JL
Alfonso AE, see Sklar GS
Ali HH, Savarese JJ, Basta SJ, Sunder N, Gionfriddo M. Tracheal intubation with vecuronium (ORG NC45) (abstract) 1984;63:177
Savarese JJ, Lebowitz PW. Twitch, tetanus, and train-of-four responses as indices of recovery from nondepolarizing neuromuscular blockade (abstract) 1980;59:524
see Basta SJ
see Brand JB
see Donlon JV Jr
see Lebowitz PW
see Ramsey FM
Ali M, see Chalon J
see O'Meara JB
Ali MM, see Chalon J
Alifimoff JK. Medicine for anaesthetists (book review) 1983;62:372
Principles and practice of blood–gas analysis (book review) 1984;63:627
Respiratory care case studies (book review) 1983;62:463
Allarde R, see Ingersoll I
see Lell WA
Allen FB, see Gerson JI
see Thomason JR
Allen GD. Dental anesthesia and analgesia (book review) 1980;59:228
Allen GW, see Frederickson EL
Allen HL. Rediscovering the larynx (letter) 1983;62:855
Allen M, see Watson J
Allen MC, see Cowen MJ
Alling CC III, Mahan PE. Facial pain (book review) 1978;57:154
Allman FD, see Baskoff JD
Alloza JL, see Weis OF
Almonte RO, see Weiss R
Alper MH, see Datta S
Althaus JS, see Woodside JR Jr
Alvaran SB, Toung JK, Graff TE, Benson DW. Venous air embolism: comparative merits of external cardiac massage, intracardiac aspiration, and left lateral decubitus position 1978;57:166
Alvis JM, see Reves JG
Amaha K, see Iwatsuki N
Amaki Y, Nagashima H, Radnay PA, Foldes FF. Ketamine interaction with neuromuscular blocking agents in the phrenic nerve-hemidiaphragm preparation of the rat 1978;57:238
Amaranath L, Andersen NB. The effect of general anesthetic agents, ouabain, and aldosterone on striated muscle contraction in toad 1976;55:409
Boutros AR. Circle absorber and soda lime contamination (letter) 1980;59:711
Cascorbi HF, Singh-Amaranath AV et al. Relation of anesthesia to total hip replacement and control of operative blood loss 1975;54:641
Amberg HL, Gordon G. Low-dose intramuscular ketamine for pediatric radiotherapy: a case report 1976;55:92
Use of monitor for ketamine in radiotherapy (correspondence) 1976;55:895
Ambre J, see Ghoneim MM
Amirdivani M, Chalon J, Ramanathan S, Turndorf H. Ethanol, diazepam, and scopolamine alter murine learning function and memory; ethanol changes halothane minimum alveolar concentration 1979;58:452
see Chalon J
see O'Meara JB
Siegel D, Chalon J, Ramanathan S, Turndorf H. A heated water humidifier with a rotating wick 1979;58:244
Ammendrup P, Atlee JL III. Mechanical hyperventilation, effect on specialized atrioventricular conduction, supraventricular refractoriness, and experimental atrial arrhythmias 1980;59:839
see Atlee JL III
Amory DW, see Sivarajan M
Andersen HW, see Benumof JL
Andersen NB, see Amaranath L
Andersen PT. Alopecia areata after epidural morphine (letter) 1984;63:1139
Andersen TW, see Lee PKY
Anderson DR. Thiopental and succinylcholine: action on intraocular pressure (guest discussion) 1975;54:474
Anderson EF. A potential ignition source in the operating room 1976;55:217
Anderson N, see Ritter JG
Anderson WW, see Belani KG
Andrade P. Monitoring sensory level during spinal and epidural anesthesia (letter) 1981;60:694
Andre JM, see Koka BV
Andree RA, Benzon HT. Sudden death following naloxone administration 1980;59:782
Blacker HM. Volitional sympathetic control 1980;59:785
see Lee HC
Andrews RW, see Conahan TJ III
see Palermo LM
Andriano KP, Pace NL, Wilbrink J, Zwanikken P, Stanley TH. Intraoperative transcutaneous $PO_2$ ($TcPO_2$) monitoring quantitates $PaO_2$. Fact or fiction? (abstract) 1984;63:178
see Bailey PL
see Liu W-S
Ang ET, Lassale B, Goldfarb G.

Continuous axillary brachial plexus block—a clinical and anatomical study 1984;63:680
Angelillo JC, see Fagraeus L
Anger C, see Van Aken H
Ansari IA, Kohli V, Kamath SA, Tempesta R. Effects of verapamil and lidocaine on hemodynamics and hormonal responses during endotracheal intubation in dogs (abstract) 1984;63:179
Anton AH, Uy DS, Redderson CL. Autonomic blockade and the cardiovascular and catecholamine response to electroshock 1977;56:46
Antonio R, see Zaidan J
Antonio RP, see Savarese JJ
Aoki A, see Kinoshita O
Aoki T, see Foldes FF
Apfelbaum JL, see Gross JB
Apfelbaum R, see Mogos B
  see Ueda I
Apostolou GA, Zarmakoupis PK, Mastrokostopoulos GT. Spread of epidural anesthesia and the lateral position 1981;60:584
Appel P, see Lippmann M
Arakawa K, see Goto H
  see Ido Y
  see Kim JM
  see Seto K
Arandia HY, Grogono AW. Comparison of the incidence of combined "risk factors" for gastric acid aspiration, influence of two anesthetic techniques 1980;59:862
  Kane PB. Peripheral vascular resistance and venous capacitance changes after thiopental administration during cardiopulmonary bypass (abstract) 1981;60:235
Archer TL, Janowsky EC. Plasma pseudocholinesterase deficiency associated with diethylstilbestrol therapy 1978;57:726
Arens JF, see Gloyna DF
  see Priano LL
Argentieri MP, see Hendrickx HHL
Arguelles JE, Franatovic Y, Romo-Salas F, Aldrete JA. Intrabiliary pressure changes produced by narcotic drugs and inhalation anesthetics in guinea pigs 1979;58:120
Arismendy J, see Ramanathan S
Arkin DB, Saidman LJ, Benumof JL. Case history number 98: hypotension following cardiopulmonary bypass 1977;56:720
Arlund C, see Henling CE
Armstrong IR, Littlewood DG, Chambers WA. Spinal anesthesia with tetracaine—effect of added vasoconstrictors 1983;62:793
Arnold B, see Hess W
Arnold JA, see Priano LL
Arnold WP. Measurement of pseudocholinesterase (letter) 1983;62:617
Aronson HB, see Vataghsky E
  see Bellotti GA
Arora S, see Aldrete JA
Arthur GR, see Pedersen H
  see Sage DJ
Artin RY, see Thompson GE
Artru AA. Effects of halothane, enflurane, isoflurane, and fentanyl on resistance to reabsorption of cerebrospinal fluid (abstract) 1984;63:180
  Michenfelder JD. Anoxic cerebral potassium accumulation reduced by phenytoin: mechanism of cerebral protection? 1981;60:41
  Michenfelder JD. Cerebral potassium release reduced by diphenylhydantoin, proposed mechanism of cerebral protection (abstract) 1980;59:535
  Michenfelder JD. Enflurane causes imbalance between CSF production and clearance (abstract) 1981;60:235
  Michenfelder JD. Influence of hypothermia or hyperthermia alone or in combination with pentobarbital or phenytoin on survival time in hypoxic mice 1981;60:867
  Michenfelder JD. Phenytoin in the treatment of cerebral ischemia (letter) 1981;60:617
  see Colley PS
Arts THM, see Vree TB
Artu AA. Effects of halothane and fentanyl on the rate of CSF production in dogs 1983;62:581
Artusio JF Jr. Numenon and the phenomenon 1975;54:257
Arvill A, see Rawal N
Asher AS, see Neuman GG
Ashok U, see Ramanathan S
Ashton, JPA, see Halperin BD
Asiddao CB, Donegan JH. Relationship of preoperative blood pressure and anesthetic technique to postoperative complications following carotid endarterectomy (abstract) 1981;60:236
  Donegan JH, Whitesell RC, Kalbfleisch JH. Factors associated with perioperative complications during carotid endarterectomy 1982;61:631
  see Abram SE
  see Whitesell R
Askanazi J, see Rosenbaum SH
Asrani R, see Choi H
Assmann DC, Hixon SJ, Kacmarek RM. Clinical simulations for respiratory care (book review) 1979;58:533
Aston R, see Garde JF
Atinault A, see Stanley TH
Atkinson ER, see Lees DE
Atkinson RS, see Lee JA
Atlee JL III, Alexander SC. Halothane effects on conductivity of the AV node and His-Purkinje system in the dog 1977;56:378
Ammendrup P. Mechanical hyperventilation and experimental atrial arrhythmias in halothane-anesthetized dogs (abstract) 1980;59:526
Ammendrup P, Malkinson CE. Halothane and hypocapnia: effects on electrically stimulated atrial arrhythmias in digitalized dogs 1981;60:302
  Laravuso RB. Muscle relaxants and high-dose fentanyl: hemodynamics during coronary bypass surgery (abstract) 1984;63:181
  see Ammendrup P
Attia RR, Grogono AW. Practical anesthetic pharmacology (book review) 1979;58:162
  Miller EV, Kitz RJ. Teaching effectiveness: evaluation of computer-assisted instruction for cardiopulmonary resuscitation 1975;54:308
Au E, see Lippmann M
Aubier M, see Milic-Emili J
Auffant RA, see Shuptrine JR
Aukburg SJ, Marshall BE, Wurzel HA, Ewing BC, Suer SF, Neufeld GR. Evaluation of the Swank IL-201 transfusion filter 1978;57:463
  see Martin DE
Auld PAM, see Scarpelli EM
Aultman DF, see Kissin I
  see Motomura S
Ausems ME, Hug CC Jr, de Lange S. Variable rate infusion of alfentanil as a supplement to nitrous oxide anesthesia for general surgery 1983;62:982
Ausinsch B, Rayburn RL, Munson ES et al. Ketamine and intraocular pressure in children 1976;55:773
Austin JC, see Vieira E
Auvinen J, see Kouttila K
Avila-Valdez E, see Toro-Matos A
Avram JF, see Fragen RJ
Avram MJ, see Shanks CA
Axelsson K, see Rawal N
Aye LS. Percutaneous transtracheal ventilation (letter) 1983;62:619
Ayub A, see Ona FV
Azar I, Cottrell J, Gupta B, Turndorf H. Furosemide facilitates recovery of evoked twitch response after pancuronium 1980;59:55
  Lear E. Cardiovascular effects of

- Azar I—*continued*
  - Lear E—*continued*
    - electroconvulsive therapy in patients taking tricyclic antidepressants (letter) 1984;63:1140
  - Patel AK, Phan CQ. Cardiovascular response following naloxone administration during enflurane anesthesia (abstract) 1981;60:237
  - Pham NA, Karenbelkar DJ, Heart rate following administration of edrophonium-glycopyrrolate and edrophonium-atropine mixtures (abstract) 1982;61:167
  - Turndorf H. Paroxysmal left bundle branch block during nitrous oxide anesthesia in a patient on lithium carbonate: a case report 1977;56:868
  - Turndorf H. Severe hypertension and multiple atrial premature contractions following naloxone administration 1979;58:524
- Babbs CF, see Ralston SH
- Babinski MF, Smith RB. High frequency positive pressure ventilation for abdominal surgery (abstract) 1984;63:182
- Bachhuber SR, see Maitra AM
- Bachman TE, Foster SL, Norton AC. Oxygen monitors (letter) 1981;60:539
- Bachmann M, see Forster A
- Backer CL, Tinker JH, Robertson DM, Vlietstra RE. Myocardial reinfarction following local anesthesia for ophthalmic surgery 1980;59:257
- Baden JM, Land PC, Egbert B, Kelley M, Mazze RI. Lack of toxicity of enflurance on male reproductive organs in mice 1982;61:19
  - Rice SA, Serra M, Kelley M, Mazze R. Thymidine and methionine syntheses in pregnant rats exposed to nitrous oxide 1983;62:738
  - see Maze M
  - see Mazze RI
- Badenhorst CH, see Weis OF
- Baele PL, McMichan JC, Marsh HM, Sill JC, Southorn PA. Continuous monitoring of mixed venous oxygen saturation in critically ill patients 1982;61:513
- Baenziger JC, see Ravindran RS
- Bagshaw RJ, Cox RH. Baroreceptor reflexes and pulmonary hemodynamics during halothane and halothane-nitrous oxide anesthesia in the dog 1981;60:701
  - see Bruno LA
- Bahn RC, see Ward EM
- Bailey DR, see Kaplan JA
- Bailey LW, see Harris JA
- Bailey PL, Andriano KP, Pace NL, Westenskow DR, Stanley TH. Small doses of fentanyl potentiate and prolong diazepam induced respiratory depression (abstract) 1984;63:183
- Bain JA, Spoerel WE. Rebreathing characteristics of Bain anesthesia circuit (correspondence) 1978;57:375
- Bainton CR, see Gerson JI
  - see Hoar PF
  - see Koblin DD
- Baker JD III, see Blackmon BB
- Baker PR, see Cuschieri A
- Baker T, see Stanec A
- Balamoutsos MG, Tsakona H, Kanakoudes PS, Iliadelis E, Georgiades CG. Alcuronium for open-eye injuries (letter) 1984;63:544
- Balamoutsos NG, Drossou FR, Alevizou FR, Tiovairi E, Papastephanou C, Marios A. Pupil size during reversal of muscle relaxants 1980;59:615
  - Papastephanou C, Skourtis HT. Potentiation and prolongation of neuromuscular blockade of pancuronium with *d*-tubocurarine (letter) 1981;60:229
  - Tsakona H, Kanakoudes PS, Iliadelis E, Georgiades CG. Alcuronium and intraocular pressure 1983;62:521
- Balcar I, see Metz S
- Baldsin D, see Watson J
- Baldwin SJ, see Ravindran RS
- Bålfors E. Hazards of ketamine in ischemic heart disease (letter) 1983;62:144
- Balfour RI, see Moore DC
- Baraka A. Intravenous lidocaine controls extubation laryngospasm in children 1978;57:506
- Bali IM, Dundee JW, Doggart JR. The source of increased plasma potassium following succinylcholine 1975;54:680
  - see Batra YK
- Balingit PE, see Park WY
- Ball CG, D'Alessandro FT, Rosenthal J et al. An unusual complication of lumbar puncture: a CSF cutaneous fistula (case history) 1975;54:691
  - see Berry FA
- Balsley S, see Eisenberg M
- Bamforth BJ, see Celesia GG
- Bander JJ, see Budassi SA
- Banner MJ, see Gallagher TJ
- Baraka A. A simple method of inserting a nasogastric tube for anesthesia (brief reports) 1976;55:303
  - Antagonism of succinylcholine-induced contracture of denervated muscles by *d*-tubocurarine 1981;60:605
  - Dajani A. Atracurium in myasthenics undergoing thymectomy 1984;63:1127
  - Maktabi M, Noueihid R. Epidural meperidine-bupivacaine for obstetric analgesia 1982;61:652
  - Muallem M, Noueihid R, Chaya L, Mouradian E. Oxygen jet ventilation of patients with tracheal T-tube (letter) 1982;61:622
  - Noueihed R, Sinno H, Wakid A, Agoston S. Succinylcholine-vecuronium (Org NC 45) sequence for cesarean section 1983;62:909
  - Oxygen-jet ventilation during tracheal reconstruction in patients with tracheal stenosis 1977;56:429
  - Posttetanic facilitation as index for antagonism of phase II block (letter) 1981;60:911
  - Saab M, Salem MR, Winnie AP. Control of gastric acidity by glycopyrrolate premedication in the parturient 1977;56:642
  - Yared JP, Karam AM, Winnie A. Glycopyrrolate-neostigmine and atropine-neostigmine mixtures affect postanesthetic arousal time differently 1980;59:431
- Baranowski DF. Manual of respiratory care procedures; Manual of pediatric respiratory care procedures (book review) 1983;62:373
- Barasch ST, Booth S, Modell JH. Hypercapnia during cyclopropane anesthesia: a case report (brief reports) 1976;55:439
- Barash PG, Kitahata LM, Mandel S. Acute cardiovascular collapse after intravenous phytonadione (brief reports) 1976;55:304
  - Bunke MC, Tilson MD, Katz JD, Cronau LH, Baue AE. The salutary effects of positive and expiratory pressure (PEEP) in experimentally induced Pseudomonas pneumonia 1979;58:208
  - Chen Y, Kitahata LM, Kopriva CJ. The hemodynamic tracking system, a method of data management and guide for cardiovascular therapy 1980;59:169
  - Dizon CT. An introducer for intraoperative percutaneous insertion of a Swan-Ganz catheter 1977;56:444
  - Giles R, Marx P, Berger H, Zaret B. Intubation: is low dose fentanyl really effective? (abstract) 1982;61:168
  - Kopriva CJ. The rate-pressure product in clinical anesthesia, boon or bane 1980;59:229
  - May M, Geha A, Hammond GL, Laks

H, Kopriva CJ. Patient transport following open heart surgery: a necessary evil? (abstract) 1981;60:238
  see Jatlow P
  see Meyers MB
  see Michaels I
  see Michaels IAL
  see Sudan NK
Barber RE, see Smith RH
Barberii J, see Calkins JM
Barbieri LT, Kaplan JA. Artifactual hypotension secondary to intraoperative transducer failure 1983;62:112
Barden J, see Gravenstein JS
Bargeron LM Jr, see Bini M
Barker RA, see Moffitt EA
Bar-Maor JA, see Monies-Chass I
Barnes A, see Lee C
Barnes BA, see Bunker JP
Barnes LF, see Morray JP
Barnes PA, see Gallagher TJ
Barnett AS, Hirshman CA. Anaphylactic reaction to cephapirin during spinal anesthesia 1979;58:337
Barnett WM. Medical emergency manual, 3rd edition (book review) 1984;63:471
Baron SH, Kohlmoos HW. Laryngeal sequelae of endotracheal intubation 1975;54:767
Barreras LM, see Maduska AL
Barretto C, Hook R, Seah CH. Use of the Tuohy needle in paramedian approach for peridural block 1977;56:582
Barros RS. Epidural blood patch (letter) 1981;60:122
Barrow RE, see Colgan FJ
Barry J, see Hirshman CA
Barsa JE, Batra M, Fink BR, Sumi SM. A comparative in vivo study of local neurotoxicity of lidocaine, bupivacaine, 2-chloroprocaine, and a mixture of 2-chloroprocaine and bupivacaine 1982;61:961
  Batra M, Fink BR, Sumi SM. Prolonged neural blockade following regional anesthesia with 2-chloroprocaine (letter) 1980;59:810
  Fink BR, Sumi SM, Calkins DF. Functional and structural changes in the rabbit vagus nerve in vivo following exposure to various hypoosmotic solutions 1982;61:912
Barsoum KN, see Estafanous FG
Bart AJ, see Carlson DW
  see Eckenhoff JE
Bartkowski RR, Horrow JC. Temperature and the potency of relaxants (letter) 1981;60:455
  McDonnell TE. Alfentanil as an anesthetic induction agent—a comparison with thiopental–lidocaine 1984;63:330
  see Martin DE
Bartle S, see Eisele V
Barton MD. Anesthetic problems with aspirin-intolerant patients 1975;54:376
Barverman B, Ivankovich AD, Lavine LM, Klowden AJ. Failure of cyanide to antagonize sodium nitroprusside in vivo in dogs 1980;59:672
Barzilay E, see Soroker D
Baselt RC. Analytical procedures for therapeutic drug monitoring and emergency toxicology (book review) 1980;59:522
Bashein G, Haschke RH, Ready LB. Electrical nerve location: numerical and electrophoretic comparison of insulated vs uninsulated needles 1984;63:919
Baskoff JD, Rogers MC, Allman FD, Burns B, Traystman RJ. Negative end-expiratory pressure and intracranial pressure (abstract) 1981;60:238
Bassell GM, Cullen CF, Fairchild MD, Kusske JA. Electrographic and behavioral effects of enflurane and halothane in the cat (abstract) 1980;59:527
  Rose DM, Bruce DL. Purity of USP medical oxygen (letter) 1979;58:441
  see Marx GF
Bassett EG, see Beers RF
Bassi JA, see Rosso P
Bassingthwaighte JB. Effect of halothane and pentobarbital anesthesia on the dispersion of indicator particles passing through the central circulation of the dog (guest discussion) 1977;56:72
Basson MD, Carlson BM. Myotoxicity of single and repeated injections of mepivacaine (carbocaine in the rat 1980;59:275
Basta SJ, Ali HH, Savarese JJ, Sunder N, Gionfriddo M, Cloutier G, Lineberry C, Cato AE. Clinical pharmacology of atracurium besylate (BW 33A): a new non-depolarizing muscle relaxant 1982;61:723
  see Ali HH
  Sunder N, Savarese JJ, Ali HH, Gionfriddo M. Clinical pharmacology of atracurium (BW 33A): a new neuromuscular blocking agent (abstract) 1982;61:169
Bastard OG, Carter JG, Moyers JR, Bross BA. Circulatory effects of isoflurane in patients with ischemic heart disease: a comparison with halothane 1984;63:635
  Carter JG, Moyers JR, Bross BA. Isoflurane versus halothane in ischemic heart disease (abstract) 1982;61:170
Bastron DR, Deutsch S. Anesthesia and the kidney (book review) 1977;56:760
Bastron RD. NaHCO$_2$ use with the administration of bank blood (questions and answers) 1976;55:274
  see Berry AJ
Batenhorst RL, see Bennett R
Bates ML, see Ravindran RS
Batra M, see Barsa JE
Batra MS, Driscoll JJ, Coburn WA, Marks WM. Evanescent nitrous oxide pneumothorax after laparoscopy 1983;62:1121
Batra RK, see Kalia PK
Batra YK, Bali IM. Corneal abrasions during general anesthesia 1977;56:363
Batrinos M, see Kaniaris P
Battit GE. Regional versus general anesthesia (questions and answers) 1976;55:277
Baue AE, see Barash PG
Bauer S, see Vaughan RW
Bauman DI, see Waller JL
Baumgartner WA, see Mihm FG
Baxter AD, Kiruluta G. Detrusor tone after epidural morphine (letter) 1984;63:464
  O'Kafo BA. Ejaculatory failure after chemical sympathectomy 1984;63:770
Baysinger CL, see Rosen MA
  see Rubin AS
Baysinger M, see Weiskopf RB
Bazaral MG, Norfleet EA. Comparison of CB$_5$ and V$_5$ leads for intraoperative electrocardiographic monitoring 1981;60:849
Beach TF, see Warner LO
Beasley JM, Jones SEF. A guide to paediatric anaesthesia (book review) 1981;60:231
Beaupre PN, see Cahalan MK
Beck HA, see Pflug AE
Beckman JJ, see Woodside JR Jr
Bedford RF, Berry FA Jr, Longnecker DE. Impact of propranolol on hemodynamic response and blood cyanide levels during nitroprusside infusion: a prospective study in anesthetized man 1979;58:466
  Clinical frontiers in anesthesiology (book review) 1984;63:377
  Feinstein BSH. Hospital admission blood pressure, a predictor for hypertension following endotracheal intubation 1980;59:367

- Bedford RF—*continued*
  - Feinstein BSH. Hypertension after endotracheal intubation, correlation with the preoperative blood pressure record (abstract) 1980;59:527
  - Increasing halothane concentrations reduce nitroprusside dose requirement 1978;57:457
  - Marshall WK, Persing JS. Rapid reduction of intracranial pressure, thiopental versus lidocaine (abstract) 1980;59:528
  - Morris L, Jane JA. Intracranial hypertension during surgery for supratentorial tumor: correlation with preoperative computed tomography scans 1982;61:430
  - Persing JA, Pobereskin L, Butler A. Lidocaine or thiopental for rapid control of intracranial hypertension? 1980;59:435
  - see Bellotti GA
  - see Friedman GA
  - see James DJ
  - see Marshall WK
  - see Perkins NAK
  - Sodium nitroprusside: hemodynamic dose-response during enflurane and morphine anesthesia 1979;58:174
- Been H, see Schmidt JF
- Beers RF, Bassett EG. Mechanisms of pain and analgesic compounds (book review) 1980;59:82
- Behl RS, see Cook TL
- Behnia R. Renal perfusion, mannitol, and nitroprusside (letter) 1979;58:156
  - Siqueira EB, Brunner EA. Sodium nitroprusside-induced hypotension: effect on renal function 1978;57:521
- Behrendt DM, see Coran AG
- Beks JWF, Bosch DA, Brock M. Intracranial pressure III (book review) 1977;56:758
- Belain KG, Anderson WW, Buckley JJ. Adverse drug interaction involving pancuronium and aminophylline 1982;61:473
  - Gilmour IJ, McComb RC, Williams A, Thompson TR. Preextubation ventilatory measurements in newborns and infants 1980;59:467
  - Buckley JJ, Gordon JR, Castaneda W. Percutaneous cervical central venous line placement 1980;59:40
  - Gilmour IJ, McComb RC, Williams A, Thompson TR. Assessment of inspiratory capacity and maximum inspiratory pressure as aids to respiratory weaning of intubated newborns and infants (abstract) 1981;60:239
- Belkin J. Atropine in physostigmine reversal of diazepam (letter) 1980;59:459
- Bell LE, Freund PR, Slattery JT. Effect of age on caudal anesthesia with bupivacaine (abstract) 1984;63:184
  - see Freund PR
- Bellotti GA, Bedford RF, Arnold WP. Fiberoptic transillumination for intravenous cannulation under general anesthesia 1981;60:348
- Bellville JW, see Conner JT
  - see Ward DS
- Belopavlovic M, see Zegveld C
- Benavides O, see Galindo A
- Bendixen HH, see Stone JG
- Bengfort JL, see Light RW
- Benhamou D, Ecoffey C, Rouby JJ, Fusciardi J, Viars P. Impact of changes in operating pressure during high-frequency jet ventilation 1984;63:19
- Benjaminsson E, Klain M. Intraoperative dual-mode independent lung ventilation of a patient with bronchopleural fistula 1981;60:118
- Bennett EJ, see Dalal FY
  - see Patel K
- Bennett GM, Stanley TH. Cardiovascular effects of fentanyl during enflurane anesthesia in man 1979;58:179
- Bennett HL, Davis HS. Nonverbal response to intraoperative conversation (abstract) 1984;63:185
- Bennett MJ, Hirshman CA. Laser fire hazards (letter) 1982;61:546
  - Mangano DT, Connelly R, Wilkinson PL, Texeira R. Propranolol levels during cardiac surgery (abstract) 1981;60:239
  - see Hermens JM
- Bennett R, Batenhorst RL, Foster TS, Griffen WO, Wright BD. Postoperative pulmonary function with patient-controlled analgesia (abstract) 1982;61:171
- Benoit PW, see Yagiela JA
- Bensen DW, Kaufman JJ, Koski WS. Theoretic significance of pH dependence of narcotics and narcotic antagonists in clinical anesthesia 1976;55:253
  - see Alvaran SB
- Bentley JB, Borel JD, Nenad RE. Influence of age on pharmacokinetics of fentanyl (abstract) 1982;61:171
  - Borel JD, Nenad RE Jr, Gillespie TJ. Age and fentanyl pharmacokinetics 1982;62:968
  - see Borel JD
  - see Vaughan RW
  - Vaughan RW. Prone positioning in obesity (letter) 1981;60:537
  - Vaughan RW, Cork RC, Gandolfi AJ. Does evidence of reductive halothane biotransformation correlate with hepatic binding of metabolites in obese patients? 1981;60:548
  - Vaughan RW, Miller MS, Calkins JM, Gandolfi AJ. Serum inorganic fluoride levels during and after enflurane anesthesia 1979;58:409
- Benumof JL, Andersen HW. Sheath introducer catheters for rapid fluid infusion (letter) 1981;60:697
  - Canada ED, Scanlon TS, Herren AL. Intravenous anesthesia and postoperative analgesia (abstract) 1981;60:240
  - see Arkin DB
  - see Berryhill RE
  - see Diamant M
  - see Katz J
  - see Mitchell SA
  - see Pease RD
  - see Ward CF
  - Trousdale FR, Alfery DD, Ozaki GT. Large catheter sheath introducers and their side port functional gauge 1981;60:216
- Benzon HT, Braunschweig R, Molloy RE. Delayed onset of epidural anesthesia in patients with back pain 1981;60:874
  - Chomka CM, Brunner EA. Treatment of reflex sympathetic dystrophy with regional intravenous reserpine 1980;59:500
  - Convulsions secondary to intravascular phenol: a hazard of celiac plexus block 1979;58:150
  - Leventhal JB, Ovassapian A. Ketamine treatment of penile erection in the operating room (letter) 1983;62:457
  - Linde HW, Molloy RE, Brunner EA. Postdural puncture headache in patients with chronic pain 1980;59:772
- Beppu WJ, see Cook TL
- Berger H, see Barash PG
- Berger JJ, Donchin M, Morgan LS, van der Aa J, Gravenstein JS. Perioperative changes in blood pressure and heart rate 1984;63:647
- Berger JM, see Stirt JA
  - Stirt JA, Sullivan SF. Enflurane, halothane, and aminophylline—uptake and pharmacokinetics 1983;62:733
- Bergman NA, see Hirshman CA
- Bergofsky EH. Perspective: the pharmacology of severe bronchial asthma (editor's choice) 1975;54:227
- Berhard WN, Yost L, Turndorf H, Danziger F. Cuffed tracheal tubes—physical and behavioral characteristics 1982;61:36

Berilla JA, see Grundy BL
Berk JL, Sampliner JE. Handbook of critical care, second edition (book review) 1982;61:626
Berkowitz S, Gold MI. Spinal anesthesia for surgery in patients with previous lumbar laminectomy 1980;59:881 (abstract) 1980;59:529
Berman L, see de Lange S
Berman LS, see Pyles ST
  Statistically significant vs clinically significant differences (letter) 1984;63:1050
Berman ML. Diazepam reversal by physostigmine (letter) 1980;59:805
  Kuhnert L, Phythyon JM, Holaday DA. Isoflurane-induced and enflurane-induced hepatic necrosis in hyperthyroid rats (abstract) 1982;61:172
Berman RA. A method for blind oral intubation of the trachea or esophagus 1977;56:866
Bernhard W, see Cottrell JE
Bernhard WN, see Paegle RD
  see Yost LC
Berninger GT, see Gooding JM
Bernstein JS, see Kotter GS
Bernstein KJ, Gangat Y, Verosky M, Vulliemoz Y, Triner L. Halothane effect on beta-adrenergic receptors in canine myocardium 1981;60:401
  Verosky M, Triner L. Halothane inhibition of canine myocardial adenylate cyclase—modulation by endogenous factors 1984;63:285
Berretti E, see Vourc'h G
Berry A. Gastric function (letter) 1980;59:807
  Renal perfusion, mannitol, and nitroprusside (letter) 1979;58:156
Berry AJ, Isaacson IJ, Kane MA, Schatz GC, Bastron RD, Maze M, Spiss CK, Rizk SF, Ronai AK, Kimovec MA. A multicenter study of the prevalence of hepatitis B viral serologic markers in anesthesia personnel 1984;63:738
  Peterson ML. Hyponatremia after mannitol administration in the presence of renal failure 1981;60:165
  see Jones JJ
Berry D, see Bini M
Berry FA, Ball CG, Blankenbaker WL. Humidification of anesthetic systems for prolonged procedures 1975;54:50
  Extubation in epiglottitis (letter) 1984;63:469
  see Bedford RF
  see Niederlehner JR
Berryhill RE, Benumof JL, Saidman LJ, Smith PC, Plumer MH. Anesthetic management of emergency cesarean section in a patient with epidermolysis bullosa dystrophica polydysplastica 1978;57:281
Berryman JR, see Spaepen MS
Bersina-Moettus L, see Dauchot PJ
Bertoni G, see Carlon GC
Besner G, see Boulanger M
Bethea HL, Gabel JC. Oxygen therapy in athletes and fireman (questions and answers) 1977;56:155
Betts EK. Operating room temperature important to infants and children (letter) 1981;60:169
  Simplified technic of air encephalography (correspondence) 1977;56:469
Bevan DR, D'Souza J, Rouse JM, Caldwell J, Dring G, Smith RL. Clinical pharmacokinetics of fazadinium bromide in renal failure in man (abstract) 1980;59:529
  Renal function in anaesthesia and surgery (book review) 1980;59:396
  see Delisle S
  see Donati F
  see Sprigge JS
Beyer CW, see Giesecke AH Jr
Beynen FM, Knopp TJ, Rehder K. Nitrous oxide exposure in the operating room 1978;57:216
Bezzo RR, see Glass PM
Bhagat BD. Mode of action of autonomic drugs (book review) 1979;58:534
Bhalerao RA, see Samsi AB
Bhat R, see Braverman B
Biava CG, see Eger EI II
  see Harper MH
Bidwai AV, see Hill GE
  see Liu WS
  see Stanley TH
  Stanley TH, Bloomer HA et al. Effects of anesthetic doses of morphine on renal function in the dog 1975;54:357
  Stanley TH, Graves CL et al. The effects of ketamine on cardiovascular dynamics during halothane and enflurane anesthesia 1975;54:588
Biegel AA. The anesthetic and perioperative management of a patient with documented hereditary angioneurotic edema (comment) 1977;56:573
Biehl DR, see Gregory GA
  Tweed A, Cote J, Wade JG, Sitar D. Effect of halothane on cardiac output and regional flow in the fetal lamb in utero 1983;62:489
  Wade JG, Tweed A, Gregory CA, Coté J. Effect of halothane anesthesia on regional blood flow and cardiac output in the fetal lamb in utero (abstract) 1981;60:241
Biersner RJ, see Harris JA
Bikhazi GB, see Brückner J
  see Burkett L
Binda RE, Cook DR, Fischer CG. Advantages of infant ventilators over adapted adult ventilators in pediatrics 1976;55:769
Bingham HG, see Modell JH
Bini M, Reves JG, Berry D, Samuelson PN, Bargeron LM Jr. Ejection fraction during ketamine anesthesia in congenital heart diseased patients (abstract) 1984;63:186
Birch AA, Boyce WH. Changing renal blood flow following sodium nitroprusside in patients undergoing nephrolithotomy 1977;56:102
  Boyce WH. Hypertension and decreased renal blood flow following methylene blue injection 1976;55:674
  Boyce WH. Renal blood flow during combination nitroprusside-dopamine infusions (abstract) 1980;59:530
  see McLeskey CH
Bircher N. Anesthesiology—problem-oriented patient management (book review) 1984;63:378
Bird TM, Stunin L. Hemodynamic monitoring (letter) 1983;62:702
Bishay EG, Fukunaga AF, Echiverri E, Smagalski G, Ito H, Webb J. Cardiovascular effects of prolonged isoflurane induced hypotension (abstract) 1984;63:187
Bishko JR, see Paul WL
Bishop MJ, Hibbard A, Vogel A, Fink BR, Weymuller EA. Laryngeal effects of prolonged intubation in the dog (abstract) 1984;63:188
  Weymuller EA Jr, Fink BR. Laryngeal effects of prolonged intubation 1984;63:335
Bishop SP, see Gelman S
Bittar D. Respiratory obstruction associated with induction of general anesthesia in a patient with mediastinal Hodgkin's disease (case history) 1975;54:399
Bitterman H, Kerem DH, Shabtaiy, Gavriely N, Palti Y. Respiration maintained by externally applied vibration and trachial insufflation in the cat 1983;62:33
Bivins BA, see Dorris GG
Bizzarri DC, see Milliken RA
Bizzarri DV, see Giuffrida JG
  see Komatsu T
Bizzarri-Schmid M, see Sheskey MC
Bjoraker DG, Ketcham TR. Catheter thrombus artifactually decreases thermodilution cardiac output measurement 1983;62:1031

Bjoraker DG—*continued*
  Knight PR, Kirsh M. Nitroglycerin during infrarenal aortic clamping (abstract) 1981;60:242
  see Jones RM
Black J, see Sparks DL
Blackmon BB, Mahaffey JE, Baker JD III. Clinical comparison of midazolam hydrochloride and midazolam maleate for anesthesia induction 1984;63:1116
Blackstone EH, see Lell WA
Blair MR Jr, see Adams HJ
Blaise G, Roy WL. Spinal anesthesia in children (letter) 1984;63:1140
Blake TM, The practice of electrocardiography (book review) 1982;61:549
Blanck TJJ. A simple closed system for performing biochemical experiments at clinical concentrations of volatile anesthetics 1981;60:435
  Gruener R, Suffecool SL, Thompson M. Calcium uptake by isolated sarcoplasmic reticulum: examination of halothane inhibition, pH dependence, and $Ca^{2+}$ dependence of normal and malignant hyperthermic human muscle 1981;60:492
  Thompson M. Enflurane and isoflurane stimulate calcium transport by cardiac sarcoplasmic reticulum 1982;61:142
  Thompson M. Measurement of halothane by ultraviolet spectroscopy 1980;59:481
Bland JW, see Kaplan JA
Blankenbaker WL, see Berry FA Jr
  The care of patients with phantom limb pain in a pain clinic 1977;56:842
Blanloeil YAG, see Pinaud MJL
Blatnick RA, see Bidwai AV
  see Hill GE
Blendinger I, see Abouleish E
Blenkarn GD. Anesthetic considerations in patients with gas gangrene (guest discussion) 1976;55:252
Blikian A, see Abboud TK
Bliss J, see Kim JM
Blitt CD, Carlson GL, Wright WA, Otto CW. J-wire versus straight wire for central venous cannulation via the external jugular vein 1982;61:536
  Catheterization techniques for invasive cardiovascular monitoring (book review) 1982;61:806
  Complete obstruction of an armored endotracheal tube (correspondence) 1975;54:350
  Droperidol and pheochromocytoma (letter) 1981;60:770
  Gandolfi AJ, Soltis JJ, Brown BR Jr. Extrahepatic biotransformation of halothane and enflurane 1981;60:129
  Petty WC, Alberternst EA, Wright BJ. Correlation of plasma cholinesterase activity and duration of action of succinylcholine during pregnancy 1977;56:78
  Petty WC. Reversal of lorazepam delirium by physostigmine 1975;54:607
  Petty WC, Wright WA et al. Clinical evaluation of injectable lorazepam as a premedicant: the effect on recall 1976;55:522
  see Gandolfi AJ
  see Geha DE
  see Hameroff SR
  see Reynolds AF
  see Stiffel P
  Succinylcholine, avoidance of side effects (questions and answers) 1975;54:637
  Weldon ST, Williams-Van Alstyne SI, Gandolfi AJ. Survey of impurities in isoflurane and enflurane vaporizers (abstract) 1984;63:189
Bloch EC, Burton LW. Electrosurgical burn while using a battery-operated Doppler monitor 1979;58:339
  Karis JH. Cardiopagus in neonatal thoracopagus twins, anesthetic management 1980;59:304
Block P, see Landry LD
Bloom MJ, see Bruno LA
Bloomer HA, see Bidwai AV
Bloor BC, Flack WE. Reduction in halothane anesthetic requirement by clonidine, an alpha-adrenergic agonist 1982;61:741
  Flacke WE. Clonidine increases cardiovascular margin of safety for halothane in dogs (abstract) 1982;61:173
  Frutkin D, Van Etten A, Flacke WE. Effect of clonidine on the tachyphylaxis of sodium nitroprusside (abstract) 1984;63:190
  see Flacke JW
  see Fukunaga AF
  see Glisson SN
Blozis GG, see Halstead CL
Blumenberg D, Homann B, Sperling M. Behavior of immune globulins in patients after autotransfusion with the Haemonetics Cell-Saver (abstract) 1981;60:242
Boba A. Anesthetic circuits and inflow requirements (correspondence) 1978;57:750
Bobko S, see Wingard DW
Bochner F, Carruthers G, Kampmann J, Steiner J. Handbook of clinical pharmacology (book review) 1978;57:753
Bodai BI, Harms BA, Nottingham PB, Zaiss C, Demling RH. The effect of ketamine on endotoxin-induced lung injury 1983;62:398
Bodily MN, see Westenskow DR
Bodman HA, see Spaepen MS
Bodner A, see Sosis M
Boehm FH, Woodruff LF, Growdon JH. The effect of lumbar epidural anesthesia on fetal heart rate baseline variability 1975;54:779
Bogard TD, see Dewan DM
Bogetz MS, see Weiskopf RB
Boghaert A, see Zegveld C
Boheler J, Hamrick JC Jr, McKnight RL, Eger EI II. Isoflurane and malignant hyperthermia (letter) 1982;61:712
Bohn DJ, see Butler WJ
Bokesch PM. Fluid and blood therapy in anesthesia (book review) 1983;62:1053
Bolan JC, see Craft JB Jr
Bollinger CW. An inexpensive blood warmer (correspondence) 1975;54:816
Bomberger RA, see Saleh SA
Bond VK, see Ravindran RS
  see Young SR
Bonica JJ, Liebeskind JC, Albe-Fessard DG. Advances in pain research and therapy (book review) 1980;59:165
  Pain—Association for Research on Nervous and Mental Disease, Volume 58 (book review) 1980;59:461
  Ventafridda V. International symposium on pain of advanced cancer—advances in pain research (book review) 1979;58:445
Bonilla O, see Galindo A
Bonin JD, see de Jong RH
Bonner JT. Oxygen therapy, athletes and firemen (questions and answers) 1977;56:155
Booij LHDJ, Edwards RP, Sohn YJ, Miller RD. Cardiovascular and neuromuscular effects of Org NC 45, pancuronium, metocurine, and *d*-tubocurarine in dogs 1980;59:26
  Miller RD, Crul JF. Neostigmine and 4-aminopyridine antagonism of lincomycin-pancuronium neuromuscular blockade in man 1978;57:316
  Miller RD, Jones MJW, Stanski DR. Antagonism of pancuronium and its metabolites by neostigmine in cats 1979;58:483
  van der Pol F, Crul JF, Miller RD. Antagonism of Org NC 45 neuromuscular blockade by neostigmine, pyridostigmine, and 4-aminopyridine 1980;59:31
Boon J, see Rocco AG
Boonstra S, see Sia RL

Booth S, see Barasch ST
Borel JD, Bentley JB, Vaughan RW, Gandolfi AJ. Enflurane blood-gas solubility: influence of weight and hemoglobin 1982;61:1006
  see Bentley JB
Borg T, see Modig J
Borg U, Eriksson I, Sjöstrand U. High-frequency positive-pressure ventilation (HFPPV), a review based upon its use during bronchoscopy and for laryngoscopy and microlaryngeal surgery 1980;59:594
  see Bunegin L
Borgstedt HH, see Dobkin AB
Borland LM. Common problems in pediatric anesthesia (book review) 1983;62:543
  Introduction to anesthesia: the principles of safe practice (book review) 1983;62:864
  Textbook of pediatric emergency medicine (book review) 1984;63:472
Bos E, see Prakash O
Bosch DA, see Beks JWF
Boscoe MJ, see de Lange S
Bosnjak ZJ, Kampine JP. The effects of halothane on transmembrane potentials, $Ca^{2+}$ transients and papillary muscle tension (abstract) 1984;63:191
  see Palmer SK
Botros SB, see Gallagher JD
Boudreaux JP, Schieber RA, Cook DR. Hemodynamic effects of halothane in the newborn piglet 1984;63:731
Bough L, see Lear E
Boulanger M, Besner G, Hudon G, Meere C. Superior vena cava obstruction—an unusual complication of heart surgery 1983;62:941
  Maillé JG, Pelletier GB, Michalk S. Vasospastic angina after calcium injection 1984;63:1124
Boulukos PA, see Miller R
Bourke DL. A question of statistics (correspondence) 1977;56:467
  Interpretation of negative results (letter) 1983;62:1045
  Lawrence J. Simultaneous monitoring of central venous and Swan-Ganz pressures (brief reports) 1975;54:549
  see Khalil SN
  see Rosenberg MB
Bourke RS, see Popp AJ
Boutros AR, see Ameranath L
Bove JR, see Myhre BA
Bovill JG, Sebel PS, Fiolet JWT, Touber JL, Kok K, Philbin DM. The influence of sufentanil in endocrine and metabolic responses to cardiac surgery 1983;62:391
  see Sebel PS
  Warren PJ, Schuller JL, van Wezel HB, Hoeneveld MH. Comparison of fentanyl, sufentanil, and alfentanil anesthesia in patients undergoing valvular heart surgery 1984;63:1081
Bowdle TA. Improved technique for placement of Sorenson CVP catheters (letter) 1984;63:1143
  see Freund PR
Bowman RE, see Quimby KL
Bowman WC. Pharmacology of neuromuscular function (book review) 1981;60:620
  Prejunctional and postjunctional cholinoceptors at the neuromuscular junction 1980;59:935
Boyan CP, Privitera PA. Resection of stenotic trachea: a case presentation 1976;55:191
  Rebreathing characteristics of Bain anesthesia circuit (correspondence) 1978;57:377
  see Chu YK
Boyce WH, see Birch AA
  see McLeskey CH
Bozeman R, see Brooks JL Jr
  see Waller JL
Brackebusch M, see Hirshman CA
Bradbury M. The concept of a blood-brain barrier (book review) 1980;59:713
Bradford MW, see Ewart RBL
Bradley EL Jr, see Gelman S
Bradshaw JJ, Ivanetich KM. Isoflurane: a comparison of its metabolism by human and rat hepatic cytochrome P-450 1984;63:805
  see Ivanetich KM
Bramis J, see Pratilas V
Bramwell RS, see Hammonds W
  see Newsome L
Brand JB, Cullen DJ, Wilson NE, Ali HH. Spontaneous recovery from nondepolarizing neuromuscular blockade: correlation between clinical and evoked responses 1977;56:55
Brandford HG, see Morray JP
Brandom BW, Brandom RB, Cook DR. Uptake and distribution of halothane on infants: in vivo measurements and computer simulations 1983;62:404
  Cook DR. Error in sampling of exhaled gases (letter) 1983;62:955
  see Cook DR
  Woelfel SK, Cook DR, Fehr BL, Rudd GD. Clinical pharmacology of atracurium in infants 1984;63:309
Brandom RB, see Brandom BW
Brannan MD, see Chu SS
Brannon WL, see Massey EW
Branthwaite MA, Anaesthesia for cardiac surgery and allied procedures, second edition (book review) 1981;60:233
Braunschweig R, see Benzon HT
Braunstein MC. Apnea with maintenance of consciousness, following intravenous diazepam 1979;58:52
Braverman BD, Bhat R, Vidyasager D, Ivankovich AD. Tissue pH monitoring during hypoxia in puppies under halothane vs pentobarbital (abstract) 1981;60:243
  Ivankovich AD, McCarthy R. The effects of fentanyl and vasopressors on anesthetized dogs receiving MAO inhibitors (abstract) 1984;63:192
  see El-Baz N
  see Ivankovich AD
Brebner J, see Drummond J
Brechner VL. Case history number 94: the treatment of chronic pain: a multi-faceted approach (comment) 1977;56:122
Breivik H, see Koller M-E
Brena SF. Case history number 94: the treatment of chronic pain: a multi-faceted approach (guest discussion) 1977;56:119
Brewis RAL. Lecture notes on respiratory disease, 2nd ed (book review) 1981;60:71
Brickler J, see Dryden GE
Bridenbaugh LD. Regional versus general anesthesia (questions and answers) 1976;55:277
  see Moore DC
  see Thompson GE
Bridenbaugh PO. A survey of the practice of anesthesiology in the U.S.—1972 1975;54:112
  Heparinization, operative, spinal anesthesia (questions and answers) 1975;54:506
  see Cousins MJ
  see Denson DD
  see Moore DC
Bright RW, see Perschau RA
Brinkman CR III, see Murad SHN
Bristow GK, see Pickering BG
Britt BA. International anesthesiology clinics, Volume 17 (book review) 1980;59:396
  see Jones PIE
Britt RH, see Cohen MS
Brittain T, see Ivanetich KM
Briwa J, see Datta S
Brock M, see Beks JWF
Brock-Utne JG, Adams B. Downing JW. Monitoring neuromuscular blockade—evaluation of a new rectal electrode/transducer system in cats 1984;63:152
  Domperidone antagonizes the relaxant effect of atropine on the lower esophageal sphincter 1980;59:921

- Brocke-Utne JG—*continued*
  - Downing JW. Rectal burn after the use of an anal stainless steel electrode/transducer system for monitoring myoneural junction (letter) 1984;63:1139
  - Downing JW, Welman S, Dimopoulos GE, Moshal MG. Lower esophageal sphincter tone during reversal of neuromuscular blockade by atropine and neostigmine 1978;57:171
  - Kallichurum S, Mankowitz E, Downing JW. Hairshaft in the subarachnoid space following lumbar puncture (letter) 1981;60:694
  - see Winning TJ
- Brodman E, Duncalf D. Avoiding the trauma of nasotracheal intubation (letter) 1981;60:618
- Brodsky JB, Abramawitz MD, Mehrez MP. Endobronchial intubation for intraoperative protection of a single functioning lung: a case report 1976;55:340
  - Clinical aspects of oxygen: International Anesthesiology Clinics, Volume 19, Number 3, Fall 1981 (book review) 1982;61:71
  - Cohen EN, Brown BW Jr, Wu ML, Whitcher CE. Exposure to nitrous oxide and neurologic disease among dental professionals 1981;60:297
  - see Coe VL
  - see Merrill DG
  - see Robson JA
  - see Shulman MS
  - see Wong AL
  - see Wyner J
  - see Wyrobek AJ
  - Wong AL, Meyer JA. Percutaneous cannulation of weakly palpable arteries 1977;56:448
- Bromage PR, Camporesi EM, Chestnut D. Epidural narcotics for postoperative analgesia 1980;59:473
  - Camporesi EM, Chestnut D. Epidural narcotics (letter) 1981;60:123
  - Camporesi EM, Durant PAC, Nielsen CH. Nonrespiratory side effects of epidural morphine 1982;61:490
  - Camporesi E, Leslie JB. Neurological effects of epidural dilaudid and methadone in volunteers (abstract) 1980;59:531
  - Epidural analgesia, (book review) 1979;58:261
  - Epidural anesthetic spread (letter) 1981;60:227
  - see Camporesi EM
  - see Steen PA
  - The price of intraspinal narcotic analgesia: basic constraints 1981;60:461
- Bromberger-Barnea B, see Stiff JL
- Brooks CG, see Margand PMS
- Brooks JL Jr, Kaplan J, Finlayson DC, Bozeman R. Vasodilators and pulmonary venous admixture after myocardial revascularization (abstract) 1980;59:532
- Bross BA, see Bastard OG
- Browder JP, see Carden E
- Brower KR, Crowell DH, Leung P, Cashman TM. Neonatal electroencephalographic patterns as affected by maternal drugs administered during labor and delivery 1978;57:303
- Brown BR. Anesthesia and the obese patient: contemporary anesthesia practice, Volume 5, (book review) 1982;61:310
  - Anesthesia and the patient with endocrine disease (book review) 1981;60:365
  - Anesthesia and the patient with heart disease (book review) 1980;59:894
  - Anesthesia and the patient with liver disease (book review) 1981;60:772
  - Intra-arterial reserpine (letter) 1980;59:889
  - Outpatient anesthesia (book review) 1979;58:352
  - see Blitt CD
  - see Gandolfi AJ
- Brown BW Jr, see Brodsky JB
- Brown CL, see Eger EI II
- Brown CQ. Inadvertent prolonged cannulation of the carotid artery 1982;61:150
  - Nicholson SA. Sheath introducer catheters for rapid fluid infusion (letter) 1981;60:696
- Brown DR, Kafer ER, Roberson VO, Wilcox BR, Murray GF. Improved oxygenation during thoracotomy with selective PEEP to the dependent lung 1977;56:26
- Brown DT, see Wildsmith JAW
- Brown EM. Intrathecal cold saline solution for intractable pain (questions and answers) 1976;55:131
  - Kunjappan V. Single needle lateral approach for lumbar sympathetic block 1975;54:725
  - Quality assurance in anesthesiology—the problem-oriented audit 1984;63:611
  - see Alexander GD
  - Single-needle lateral approach for lumbar sympathetic block (correspondence) 1976;55:451
- Brown FF III, Owens WD, Felts JA, Spitznagel EL Jr, Cryer PE. Plasma epinephrine and norepinephrine during anesthesia, enflurane-$N_2O$-$O_2$ compared to fentanyl-$N_2O$-$O_2$ (abstract) 1980;59:532
  - Owens WD, Felts JA, Spitznagel EL Jr, Cryer PE. Plasma epinephrine and norepinephrine levels during anesthesia: enflurane-$N_2O$-$O_2$ compared with fentanyl-$N_2O$-$O_2$ 1982;61:366
  - see McKleskey CH
- Brown JL, see Rubin AS
- Brown KF, see Walker JS
- Brown RC. Perchance to dream (book review) 1982;61:71
- Brown RH, see Grundy BL
  - see Pathak KS
- Brown SS, Mitchell FL, Young DS. Chemical diagnosis of disease (book review) 1981;60:365
- Brown TCK, Fisk GC. Anaesthesia for children (book review) 1980;59:397
- Brown TR, see Ravindran RS
- Brown WU Jr. Neonatal neurobehavioral tests following vaginal delivery under ketamine, thiopental, and extradural anesthesia (guest discussion) 1977;56:552
  - see Datta S
- Browne AB, see Graves CL
- Browne AF, see Abajian JC
- Browning SK, see Debrand M
- Bruce C, see Leighton KM
- Bruce DL. Alcoholism and anesthesia 1983;62:84
  - Functional toxicity anesthesia (book review) 1981;60:125
  - see Bassell GM
  - see Epstein HM
  - Stanley TH. Research replication may be subject specific (letter) 1983;62:617
- Brückner J, Thomas KC Jr, Bikhazi GB, Foldes FF. Neuromuscular drug interactions of clinical importance 1980;59:678, (abstract) 1980;59:533
- Bruderman I, see Soroker D
- Bruner JMR. Handbook of blood pressure monitoring, (book review) 1979;58:353
  - Laryngoscope bulb, electrical hazard (questions and answers) 1975;54:505
  - Peripheral nerve stimulator (questions and answers) 1975;54:297
  - Safety in operation of rechargeable ECG monitor (Tektronix) (questions and answers) 1976;55:613
  - Use of electrocautery during operation following ether skin prep (questions and answers) 1975;54:210
- Brunner EA. Absence of autoregulation of cerebral blood flow during halothane and enflurane anesthesia (guest discussion) 1976;55:106

  Ostheimer G, Stanley T. Brunner J, Dannemiller F. Efficacy and safety of cimetidine in surgical patients (abstract) 1981;60:244
  see Behnia R
  see Benzon HT
  see Cheng SC
  see Eckenhoff JE
  see Fragen RJ
Brunner EE, see Ovassapian A
Brunner J, see Brunner EA
Bruno LA, Smith DS, Bloom MJ, Domino K, Bagshaw RJ, Star AM, Cohen AM, Lupo SE. Sudden hypotension with a test dose of chymopapain 1984;63:533
Bryan AC, see Butler WJ
  see Froese AB
  see Kolton M
Bryan-Brown CW, see Hooks PJ
Buakham C, Kim JM. Cannulation of a nonpalpable artery with the aid of a Doppler monitor 1977;56:125
  see Kim JM
Buckley FP, Fink BR. Duration of action of nerve blocks produced by mixtures of local anesthetics and low molecular weight dextran: studies in rat infraorbital nerve blocks 1981;60:142
Buckley JJ, see Belani KG
Budassi SA, Bander JJ, Kimmerle L, Eie KF. Cardiac arrest and CPR (book review) 1981;60:232
Buffington C, see Sivarajan M
Buffington CW, see Glauber DT
Buffington DW, Ramanathan S, Turndorf H. Detection of anesthesia machine faults 1984;63:79
Bukowski EM, see Camporesi EM
Bulas BJ, see Aleniewski MI
Bull BS, see Moorehead MT
Bull JM, see Lees DE
Bullard JR, Houghton FM. Epidural steroid treatment of acute herniated nucleus pulposus 1977;56:862
  Hyperbaric bupivacaine peridural anesthesia in obstetrics 1978;57:593
Bullingham RES, O'Sullivan G, McQuay H, Poppleton P, Rolfe M, Evans P, Moore A. Perineural injection of morphine fails to relieve postoperative pain in humans 1983;62:164
  see Cowen MJ
  see McQuay H
  see O'Sullivan GM
  see Watson J
Bunegin L, Borg U, Sjöstrand UH. A simple fleuric high frequency jet ventilator (letter) 1983;62:122
  see Hoff BH
Bunke MC, see Barash PG
Bunker JP, Barnes BA, Mostellar F. Costs, risks, and benefits of surgery (book review) 1978;57:152
Buoncristiani RD, see Yagiela JA
Burchiel KJ, Stockard JJ, Calverley RK, Smith NT. Relationship of pre- and postanesthetic EEG abnormalities to enflurane-induced seizure activity 1977;56:509
  Stockard JJ, Calverley RK, Smith NT, School ML, Mazze RI. Electroencephalographic abnormalities following halothane anesthesia 1978;57:244
Burgess GE III, Cooper JR, Marino RJ, Peuler MJ. Anesthetic management of combined cesarean section and excision of pheochromocytoma 1978;57:276
Burke CB. More on anesthetic terminology (letter) 1982;62:623
Burkett L, Bikhazi GB, Thomas KC Jr, Rosenthal DA, Wirta MG, Foldes FF. Mutual potentiation of the neuromuscular effects of antibiotics and relaxants 1979;58:107
Burnett LL, see Moore DC
Burney RG, DiFazio CA, Foster JA. Effects of pH on protein binding of lidocaine 1978;57:478
  DiFazio CA. Hepatic clearance of lidocaine during $N_2O$ anesthesia in dogs 1976;55:322
  see DiFazio CA
  see Korevaar WC
  see Moore PA
  Winn R. Increased cerebrospinal fluid pressure during laryngoscopy and intubation for induction of anesthesia 1975;54:687
Burns B, see Baskoff JD
Burns RS, see Lee VC
Burri C, Ahnefeld FW. The caval catheter, (book review) 1979;58:160
Burrow SR, see Lalka D
Burrows FA, Seeman RG. Ketamine and myoclonic encephalopathy of infants (Kinsbourne syndrome) 1982;61:873
Burt RAP, see Davie IT
Burton LW, see Bloch EC
  see Karis JP
Bush WH, see Moore DC
Bushman JA, see Payne JP
Bussell JA, see Moffitt EA
  see Sethna DH
Butler A, see Bedford RF
  see Delaney TL
Butler B. Pulmonary air embolism and nitrous oxide challenge (letter) 1982;61:956
Butler D, see Gelfman SS
Butler WJ, Bohn DJ, Bryan AC, Froese AB. Ventilation by high-frequency oscillation in humans 1980;59:577
Buzello W, Williams CH, Chandra P, Watkins ML. Preliminary studies on the response of malignant hyperthermia susceptible pigs to vecuronium (abstract) 1984;63:193
Byck R, see Jatlow P
Byer DE. Color atlas of human anatomy (book review) 1983;62:703
  see Rorie DK
Byrd SE, see Huntington CT
Byrick RJ, Hobbs EG, Kay JC. Extrathoracic cuff pressure reflects changes of intrathoracic large airway circumference 1982;61:693
  Hobbs EG, Martineau R, Noble WH. Nitroglycerin relaxes large airways 1983;62:421
Caburnay FS, see Cuasay OS
Cahalan MK, Kremer PF, Beaupre PN, Lurz FW, Roizen MF, Cronnelly R, Robinson S, Hamilton WK, Eger EI II, Schiller NB. Consistency and reproducibility of transesophageal two-dimensional echocardiography (abstract) 1984;63:194
  see Fassoulaki A
Cairns AM, see Ogawa S
Cairoli VJ, Ivankovich AD, Vucicevic D, Patel K. Succinylcholine-induced hyperkalemia in the rat following radiation injury to muscle 1982;61:83
Calabro JR, see Stone JG
Calcaterra TC, see Carden E
Caldera DL, see Teplick R
Caldwell C, see Tyler E
Caldwell CB, see Gross JB
Caldwell J, see Bevan DR
Caldwell NJ, see Fragen RJ
Calkins DF, see Barsa J
Calkins JM, see Hameroff SR
  see Otto CW
  see Waterson CK
  see Bentley JB
  Vaughan RW, Cork RC, Barberii J, Eskelson C. Effects of dilution, pressure, and apparatus on hemolysis and flow rate in transfusion of packed erythrocytes 1982;61:776
  Waterson CK, Hameroff SR, Harris TR, Jones JF. A simple flueric high frequency jet ventilator 1982;61:138
  Waterson CK, Hameroff SR, Kanel J. Jet pulse characteristics for high-frequency jet ventilation in dogs 1982;61:293
  Waterson CK. A simple flueric high frequency jet ventilator (letter) 1983;62:123
Callaghan ML, see Waldman J
Calverley RK, see Burchiel KJ
  see Eger EI II

Calverley RK—*continued*
  see Storms LH
  Smith NT, Jones CW, Prys-Roberts C, Eger EI II. Ventilatory and cardiovascular effects of enflurane anesthesia during spontaneous ventilation in man 1978;57:610
  Smith NT, Prys-Roberts C, Eger EI II, Jones CW. Cardiovascular effects of enflurane anesthesia during controlled ventilation in man 1978;57:619
Camenzind T, see Klein SL
Cameron CB, Robinson S, Gregory GA. The minimum anesthetic concentration of isoflurane in children 1984;63:418
Cameron JL, see Chen CT
Cameron PD, McMichan JC. Percutaneous transtracheal ventilation simplified (letter) 1984;63:168
  McMichan JC. Prevention of hypoxemia during endotracheal suctioning (abstract) 1984;63:195
Camey M, see Vourc'h G
Campbell RL, see Gregg JM
  see Stoelting RK
  Small EW, Lesesne HR, Levin KJ, Moore WH. Fatal hepatic necrosis after halothane anesthesia in a boy with juvenile rheumatoid arthritis: a case report 1977;56:589
Campfield PB, see Carlon GC
Campkin TV, Turner JM. Neurosurgical anaesthesia and intensive care (book review) 1981;60:170
Campman KL, see Drain CB
Camporesi EM, Bromage PR, Durant PAC, Nielsen CH, Bukowski EM. Side effects of epidural morphine (abstract) 1982;61:174
  see Bromage PR
  see Steen PA
Camu F, Gepts E, Rucquoi M, Heykants J. Pharmacokinetics of alfentanil in man 1982;61:657
Canada ED, see Benumof JL
Cañas MS, see Krantz EM
Cant JW, see Flacke JW
Cant WF, Tinker JH, Tarhan S. Bronchial blockade in a child with a bronchopleural-cutaneous fistula using a balloon-tipped catheter (brief reports) 1976;55:874
Capan LM, Ramanathan S, Chalon J, O'Meara JB, Turndorf H. A possible hazard with use of the Ohio Ethrane vaporizer 1980;59:65
  Satyanarayana TV, Patel KP, Turndorf H, Ramanathan S. Assessment of neuromuscular blockade with surface electrodes 1981;60:244
  see Chalon J
  see Ramanathan S
  see Satyanarayana TV
  see Tanguturi S
  Turndorf H, Patel C, Ramanathan R, Acinapura A, Chalon J. Optimization of arterial oxygenation during one-lung anesthesia 1980;59:847
Caplan RA, Long MC. Balanced anesthesia does anesthetize (letter) 1984;63:1049
  Long MC. Prolonged anesthesia—management and sequelae of a two-day general anesthetic 1984;63:353
  Su JY. Differences in threshold for protamine toxicity in isolated atrial and ventricular tissue 1984;63:1111
Capps RT. ASA classification (questions and answers) 1976;55:614
Capuano C, see Giffin JP
Carden E, Browder JP, Fischer ND. Teflon injection of vocal cords under general anesthesia: a new method 1975;54:739
  Calcaterra TC, Lechtman A. Pneumatocele of the larynx: a complication of percutaneous transtracheal ventilation (brief reports) 1976;55:600
  Friedman D. Further studies of manually operated self-inflating resuscitation bags 1977;56:202
  Galido J. Foot-pedal control of jet ventilation during bronchoscopy and microlaryngeal surgery, Brief Reports 1975;54:405
  Hughes T An evaluation of manually operated self-inflating resuscitation bags 1975;54:133
  Jet ventilation for microlaryngoscopic procedures: a further simplified technic 1975;54:345
  see Raj PP
Caritis S, see Kang YG
Carlon GC, Kahn RC, Bertoni G, Campfield PB, Howland WS, Goldiner PL. Rapid volume expansion in patients with interstitial lung diseases 1979;58:13
  see Kahn RC
  see Shoum S
Carlson BM, see Basson MD
  see Foster AH
Carlson DW, Engelman DR, Bart AJ. Epidural anesthesia for cesarean section in kyphoscoliosis 1978;57:125
Carlson GL, see Blitt CD
Carlsson C, Islander G. Silent gastropharyngeal regurgitation during anesthesia 1981;60:655
Caron D, see Zegveld C
Caron J. Medical student views of anesthesiology (letter) 1979;58:443
Carr DB, see Steinbrook RA
Carrier O, Shibata S. Factors influencing vascular reactivity (book review) 1978;57:600
Carroll J. Pediatric anesthesia volume 1 (book review) 1984;63:626
Carron H, Litwiller R. Stellate ganglion block 1975;54:567
  see Delaney TJ
  see Simon GL
  see Stilz RJ
  Single-needle lateral approach for lumbar sympathetic block (correspondence) 1976;55:451
Carrow DJ, Aldrete JA, Masden RR et al. Effects of large doses of intravenous atropine on heart rate and arterial pressure of anesthetized patients 1975;54:262
  see Aldrete JA
Carruthers G, see Bochner F
Carter GL, Downs JB, Dannemiller FJ. "Hyper-" end-expiratory pressure in the treatment of adult respiratory insufficiency: a case report 1975;54:31
Carter JD, see Venkateswarlu T
Carter JG, see Bastard OG
  see Comstock MK
  see Pochanapring A
Cartwright P, Prys-Roberts C, Gill K, Dye A, Stafford M, Gray A. Ventilatory depression related to plasma fentanyl concentrations during and after anesthesia in humans 1983;62:966
Caruso FS, see Tavakoli M
Caruthers TE, see Gallagher TJ
Cascorbi HF, see Geiger RS
  see Hall RL
  see Miller JM
  see Pathak KS
  see Singh-Amaranath L
  What are the health hazards for anesthesiologists? (editorial) 1978;57:293
Casement BA, Danielson DR. The epidural blood patch: are more than two ever necessary? 1984;63:1033
Casey LC, see Chernow B
Cashman TM, see Brower KR
Casson H, see Hirshman CA
Castagnoli N Jr, see Upton RA
Castanas E, see Kaniaris P
Castaneda AR, see Hickey PR
Castaneda W, see Belani KG
Casthely P, Chalon J, Ramanathan S, Turndorf H. Tracheobronchial cytologic changes during prolonged cannulation 1980;59:759
Casthely PA, Lear S, Cottrell JE, Lear E. Intrapulmonary shunting during induced hypotension 1982;61:231

  see Fyman PN
Castresana MR, see Smith GA
Cato AF, see Basta SJ
Cattran CB, see Kolton M
Cazalaa JA, see Stanley TH
Ceballos R, see Corssen G
  see Yanagida H
Cecil WT, see Fibuch EE
Celesia GG, Bamforth BJ, Chen RC. Ketamine and epilepsy (correspondence) 1976;55:445
Cerine FC, see Sung YF
Cestone KJ, Ryan WP, Loving CD. An anesthetic gas scavenger for the Jackson-Rees system (brief reports) 1976;55:881
Chadwick K, see Weiskopf RB
Chaignon M, see Tannieres M-L
Chalon J, Ali M, Turndorf H, Fischgrund GK. Humidification of anesthetic gases (book review) 1981;60:772
  Goldman C, Amirdivani M, Rothblatt A, Ramanathan S, Turndorf H. Humidification in a modified circle system 1979;58:216
  Hillman D, Gross S, Eisner M, Tang CK, Turndorf H. Intrauterine exposure to halothane increases murine postnatal autotolerance to halothane and reduces brain weight 1983;62:565
  Markham JP, Ali MM, Ramanathan S, Turndorf H. The Pall ultipor breathing circuit filter—an efficient heat and moisture exchanger 1984;63:566
  Ramanathan S, Capan L. Rebreathing characteristics of Bain anesthesia circuit (correspondence) 1978;57:378
  see Amirdivani M
  see Capan LM
  see Cottrell JE
  see O'Meara JB
  see Paspa P
  see Ramanathan S
  see Satyanarayana T
  see Sivakumaran C
  see Tang CK
  Simon R, Patel C, Ramanathan S, Sessler S, Turndorf H. An infant circuit with a water vaporizer warmed by carbon dioxide neutralization 1978;57:307
  Tang CK, Ramanathan S, Eisner M, Katz R, Turndorf H. Exposure to halothane and enflurane affects learning function of murine progeny 1981;60:794
Chambers WA, Littlewood DG, Logan MR, Scott DB. Effect of added epinephrine on spinal anesthesia with lidocaine 1981;60:417
  Littlewood DG, Scott DB. Spinal anesthesia with hyperbaric bupivacaine: effect of added vasoconstrictors 1982;61:49
  see Armstrong JR
  see Ravindran RS
  see Scott DB
Chander S. A new head strap 1980;59:457
Chandra P, see Buzello W
  see Snow JC
Chang JL, see Albin MS
Chapin JW, Kahre J, Newland M. Acute myocardial ischemia caused by mediastinal chest tube suction 1980;59:386
  Kahre J. Progeria and anesthesia 1979;58:424
  Nance P, Yarbrough JW. Facial paleness (letter) 1982;61:475
Chapman CR, see Gehrig JD
  see Schimek F
Chapman J, see Seifen AB
Chase CR, Merz BA, Mazuzan JE. Computer assisted patient evaluation (CAPE): a multi-purpose computer system for an anesthesia service 1983;62:198
Chassy J, see Dubois MY
Chatterjee K, see Wilkinson PL
Chatterji S, see Shrivastava OP
  see Verma RS
Chaudry I, see Matsuo S
Chaya L, see Baraka A
Chelly J, see Rogers K
  see Tannieres ML
Chen ACN, see Dworkin SF
Chen CT, Toung TJK, Haupt HM, Hutchins GM, Cameron JL. Evaluation of the efficacy of Alka-Seltzer Effervescent in gastric acid neutralization 1984;63:325
Chen J, see Kareti RKP
Chen RC, see Celesia GG
Chen Y, see Barash PG
Cheney FW, see Tyler DC
Cheng A, see Shingu K
Cheng SC, Brunner EA. Neurochemical hypothesis for halothane anesthesia 1975;54:242
Chenoweth MB. Hepatitis after use of two different fluorinated anesthetic agents (correspondence) 1975;54:125
Cherniack RM, see Petty TL
Chernow B, Holbrook P, D'Angona DS Jr, Zaritsky A, Casey LC, Fletcher JR, Lake CR. Epinephrine absorption after intratracheal administration 1984;63:829
Cherry D, see Hoff BH
Chester MH. Modified Dawkins epidural indicator (letter) 1979;58:350
  Modified Dawkins epidural indicator: a useful teaching aid 1978;57:736
Chestnut D, see Bromage PR
Chestnut JS, see Newfield P
Chilcoat RT, see Patil VU
Ching KS, Ciobanu M. Prevention of succinylcholine-induced hyperkalemia by diazepam, hexafluorenium, and dantrolene (abstract) 1981;60:245
Chinthagada M, see Rao TLK
Chinyanga HM. Positioning the ultrasonic Doppler flow detector probe in small children (letter) 1982;61:69
Chiovari CA, see Hertz R
Chiu TM, Meyers EF. Defective disposable endotracheal tube (brief reports) 1976;55:437
Chodoff P, see Margand PMS
  see Siegel JH
Choi H, Asrani R, Tremper KK, Scruggs R, Cullen BF. Continuous transcutaneous $PCO_2$ monitoring during epidural analgesia (abstract) 1984;63:196
Choi WW, Mehta M, Gergis S, Sokoll M. Effect of age on neuromuscular agents (abstract) 1984;63:197
  see Ghoneim MM
Choita J Jr, see Kondo K
Chomka CM, see Benzon HT
Chretien PB, see Cullen BF
Christensen NJ, see Hasselstrøm LJ
Christian CM, Fagraeus L, Van Trigt P, Spray TL, Pasque MK. $ID_{20}$: defining myocardial depression in dogs (abstract) 1982;61:174
Christoffersson E, see Rawal N
Chu LSW, Yeh SDJ, Wood DD. Acupuncture manual, a western approach (book review) 1980;59:397
Chu SS. Plasma concentration of lidocaine after endotracheal spray (correspondence) 1976;55:117
  Rah KH, Brannan MD et al. Plasma concentration of lidocaine after endotracheal spray 1975;54:438
Chu YK, Rah KH, Boyan CP. Is the Bain breathing circuit the future anesthesia system? an evaluation 1977;56:84
Churchill-Davidson HC. A practice of anaesthesia (book review) 1979;58:163
Ciesla N, see Mackenzie CF
Cimochowski G, see Kapur PA
Ciobanu M, see Ching KS
Civetta JM. Filters used during massive blood transfusions (questions and answers) 1975;54:45
  see Gallagher TJ
Cizmar S, see Kaplan R
Clark CC, Weeks DB, Gusdon JP. Venous carbon dioxide embolism during laparoscopy 1977;56:650
Clark DL, see Gallagher JD
  see Moore RA
Clark DW, see Dworkin SF
Clark RB. Reducing the risk of acid

Clark RM—*continued*
  aspiration during cesarean section (correspondence) 1975;54:241
  see Smith DB
Clark RW, see Samuels SI
Clark WC, see Yang JC
Clarke RSJ, see Mirakhur RW
Clarkson CW, Hondeghem L, Matsubara T, Levinson G. Possible mechanism of bupivacaine toxicity: fast inactivation block with slow diastolic recovery (abstract) 1984;63:199
Cleary JL, see Hartigan ML
Cleaton-Jones P, see Vieira E
Clement HL, see Knill RL
Clement J, see Knill R
Clements J, see Lees DE
Clifford C, see Vender JS
Cline PJ, see Ravindran RS
Cloutier G, see Basta SJ
Co EG, see Craft JB
Coakley CS. Premedication, atropine (questions and answers) 1975;54:716
Coaldrake LA, see Craft JB Jr
Cobb ML, Vaughan RW. Severe hypertension in a child with Wilms' tumor: a case report 1976;55:519
Coburn WA, see Batra M
Coe VL, Brodsky JB, Mark JBD. Double-lumen endobronchial tubes for patients with tracheostomies (letter) 1984;63:882
Coetzee A, Holland D, Foëx P, Ryder A, Jones L. The effect of hypoxia on coronary blood flow and myocardial function in the dog 1984;63:991
Coeytaux R, see Stanley TH
Coggins CH, see de Lange S
  see Kono K
Cohen AM, see Bruno LA
Cohen EN. Anesthetic exposure in the workplace (book review) 1980;59:713
  Congenital abnormality in the children of exposed operating room personnel (questions and answers) 1976;55:760
  see Brodsky JB
  see Wyrobek AJ
  Toxicity of inhalation anesthetics (correspondence) 1978;57:595
  Van Dyke RA, Trudell JR. Metabolism of volatile anesthetics (book review) 1977;56:880
Cohen GR, see Kapur PA
Cohen HB, Gambill AF, Eggers GWN Jr. Acute pulmonary edema following head injury: two case reports 1977;56:136
Cohen JA, Frederickson EL, Kaplan JA. Plasma heparin activity and antagonism during cardiopulmonary bypass with hypothermia 1977;56:564
Cohen JL, see Chu SS
Cohen ML, Geraghty DM, Jackson R. A new "continuously-on" suction valve (brief reports) 1975;54:695
Cohen MR, see Lee VC
Cohen MS, Britt RH. Effects of sodium pentobarbital, ketamine, halothane, and chloralose on brainstem auditory evoked responses 1982;61:338
Cohen NH, see Forbes AR
Cohen PJ, see Knapp R
  see Knight PR
Cohn ML, see Huntington CT
Colby T, see Shulman MS
Coleman A, see Fraley DS
Coleman CC, see Hasbrouck JD
Coleman RL, see Moore DC
Coles JR, see Smith NT
Colgan FJ, Liang JQ, Barrow RE. Noninvasive assessment by capacitance respirometry of respiration before and after extubation 1975;54:807
  TenEyck LG, Sawa J. Ventilatory requirements during high frequency ventilation in dogs (abstract) 1982;61:175
Colley PS, Artru AA. ECG-guided placement of Sorenson CVP catheters via arm veins 1984;63:953
  Artru AA. EKG-guided placement of CVP catheters via arm veins: success rate, placement time, and optimal conductive solutions (abstract) 1984;63:200
  Dunn R. Prevention of blood pressure response to skull-pin head holder by local anesthesia 1979;58:241
  Sivarajan M. Regional blood flow in dogs during halothane anesthesia and controlled hypotension produced by nitroprusside or nitroglycerin 1984;63:503
Collins JG, Kitahata LM, Homma E, Suzukawa M. Spinal cord effects of epinephrine (letter) 1981;60:913
  see Akutagawa T
  see Homma E
  see Kawahara M
  see Kikuchi H
  see Kitahata LM
Collins JR. Intrathecal cold saline solution for intractable pain (questions and answers) 1976;55:131
  see Hunt JR
Collins M, see Rosen MA
Collins PA, see Eger EI II
  see Harper MH
  see Koblin DD
Collins VJ. Principles of anesthesiology (2nd ed) (book review) 1977;56:172
Colliver JA, see Manchikanti L
Colpitts YH, see Gehrig JD
  see Schimek F
Colton T, see Coombs DW
Colvin MP, see Dunnill RPH
Comer PB, see Scuderi PE
  see Weeks DB
Comroe JH Jr. Retrospectroscope: insights and medical discovery. (book review) 1978;57:290
Comstock MK, Carter JG, Moyers JR, Stevens WC. Rigidity and hypercarbia associated with high dose fentanyl induction of anesthesia (letter) 1981;60:362
Conahan TJ, Andrews RW, MacVaugh H III. Cardiovascular effects of protamine sulfate in man 1981;60:33
  see Otto CW
  Cardiac anesthesia (book review) 1982;61:720
Concepcion MA, Maddi R, Francis D, Rocco AG, Murray E, Covino BG. Vasoconstrictors in spinal anesthesia with tetracaine—a comparison of epinephrine and phenylephrine 1984;63:134
  see Rocco AG
Conklin KA, see Murad SHN
Conkloin CM, see Sethna DH
Conner JT, Bellville JW, Wender R, Schehl D, Dorey F, Katz RL. Morphine, scopolamine, and atropine as intravenous surgical premedicants 1977;56:606
  Bellville JW, Wender RH, Wapner S, Dorey FJ, Katz RL. Morphine and promethazine as intravenous premedicants 1977;56:801
  Bellville JW, Wender RH, Wayner S, Katz RL. Evaluation of intravenous diazepam as a surgical premedicant 1977;56:211
  Katz RL, Pagano RR, Graham CW. RO 21-3981 for intravenous surgical premedication and induction of anesthesia 1978;57:01
  Miller JD, Katz RL. Isoflurane anesthesia for pheochromocytoma: a case report 1975;54:419
Conolly ME, see Stirt JA
Cook DR, Brandom BW. Enflurane, halothane, and isoflurane inhibit removal of 5-hydroxytryptamine from the pulmonary circulation 1982;61:671
  Brandom BW, Shiu G, Wolfson B. The inspired median effective dose, brain concentration at anesthesia, and cardiovascular index for halothane in young rats 1981;60:182
  Brandom BW, Woelfel SK, Fehr B, Rudd D. Atracurium infusion in children during fentanyl,

halothane, and isoflurane anesthesia (abstract) 1984;63:201
  Fischer CG. Characteristics of succinylcholine neuromuscular blockade in neonates 1978;57:63
  Howell RE, Gillis CN. Xanthine oxidase-induced lung injury inhibits removal of 5-hydroxytryptamine from the pulmonary circulation 1982;61:666
  Muscle relaxants in infants and children 1981;60:335
  see Binda RE
  see Boudreaux JP
  see Brandom BW
Cook GL, see Wong KC
Cook TL, Beppu WJ, Hitt BA et al. A comparison of renal effects and metabolism of sevoflurane and methoxyflurane in enzyme-induced rats 1975;54:829
  Eger EI II, Behl RS. Is your vaporizer off? 1977;56:793
  see Hitt BA
  Smith M, Winter PM, Starkweather JA, Eger EI II. Effect of subanesthetic concentrations of enflurane and halothane on human behavior 1978;57:434
Cooke JE, Hood JB, Thomas JD. A method for inserting the Carden tube (brief reports) 1976;55:882
Coombs DW. Acid aspiration: recurring myths (letter) 1984;63:700
  Aspiration pneumonia prophylaxis (editorial) 1983;62:1055
  Hooper D, Colton T. Pre-anesthetic cimetidine alteration of gastric fluid volume and pH 1979;58:183
Coombs JHB, see Mulroy MF II
Cooper ES, see Diaz JH
Cooper JR, see Burgess GE III
Coppel DL, see Mirakhur RW
Coran AG, Behrendt DM, Weintraub WH, Lee DC. Surgery of the neonate, (book review) 1979;58:261
Corbascio AN, see Smith NT
Corbett TH. Behavioral consequences in rats from chronic exposure to 10 ppm halothane during early development (guest discussion) 1975;54:632
  see Eger EI II
  Stedmann DH. Breathalyzer test and exposure to anesthetic gases (questions and answers) 1976;55:615
  Ventilating systems in operating rooms (questions and answers) 1975;54:297
Cord RC, see Vaughan RW
Cordes RA, Eagle T. Near drowning: a complication of computerized axial tomography of the head 1978;57:359
Cork RA, Vaughan RW, Humphrey LS. Precision and accuracy of intraoperative temperature monitoring 1983;62:211
Cork RC, see Bentley JB
  see Calkins JM
  see Hameroff SR
  see Vaughan MS
  Vaughan RW. Incision, position, and time effects on postoperative hypoxemia in the morbidly obese (abstract) 1980;59:534
  Weiss JL, Hameroff SR, Bentley JB. Fentanyl preloading for rapid-sequence induction of anesthesia 1984;63:60
Corke BC, see Saltzman LS
Corrall IM, see Strunin L
Correll JW, see Rampil IJ
Corssen G, Holcomb MC, Moustapha I, Langford K, Vitek JJ, Ceballos R. Alcohol-induced adenolysis of the pituitary gland: a new approach to control of intractable cancer pain 1977;56:414
  Neuroleptanalgesia and anesthesia (correspondence) 1975;54:347
  see Gooding JM
  see Ingersoll I
  see Sparks DL
  see Tavakoli M
  see Yanagida H
Cosman EB, see Shah NK
Cosmi EV. Obstetric anesthesia and perinatology (book review) 1981;60:773
Costandi J, see Abboud TK
Coté CJ, Goudsouzian NG, Liu LMP, Dedrick DF, Firestone S. Thiopental: a dose-response study in unpremedicated children (abstract) 1981;60:246
  see Goudsouzian NG
Cote DD, see Mutch WAC
  Torchia MG. Nitroglycerin absorption to polyvinylchloride seriously interferes with its clinical use 1982;61:541
Coté J, see Biehl DR
  see Gregory GA
Cote ME, see Lebowitz PW
Cotev S, see Perel A
Cotton BR, see Hunt PCW
Cottrell JE, see Azar I
  Bernhard W, Turndorf H et al. Hazards of disposable rebreathing circuits (brief reports) 1976;55:743
  Chalon J, Turndorf H. Faulty anesthesia circuits: a source of environmental pollution in the operating room 1977;56:359
  Hartung J, Giffin JP, Shwiry B. Intracranial and hemodynamic changes after succinylcholine administration in cats 1983;62:1006 1984;63:1005
  Hartung J, Giffin JP, Shwiry B. Succinylcholine and intracranial pressure—a cause for "pause" (letter) 1984;63:620
  Occupational hazards to operating room and recovery room personnel, International Anesthesiology Clinics, Volume 19 (book review) 1982;61:549
  see Casthely PA
  see Estilo AE
  see Giffin JP
  see Seravalli EE
  Turndorf H. Anesthesia & neurosurgery (book review) 1980;59:462
  Wolfson B, Siker ES. Changes in airway resistance following droperidol, hydroxyzine, and diazepam in normal volunteers 1976;55:18
Cottrell WM, Schick LM, Perkins HM, Modell JH. Hemodynamic changes after intercostal nerve block with bupivacaine-epinephrine solution 1978;57:492
Couch NP, see Young AE
Coumans WA, see van der Vusse GJ
Cousins CL, see Moffitt EA
Cousins MJ, Bridenbaugh PO. Neural blockade in clinical anesthesia and management of pain (book review) 1981;60:232
  see Plummer JL
Couto da Silva JM, Tubino PJ, Vieira ZEG, Saraiva RA. Closed circuit anesthesia in infants and children 1984;63:765
Coveler LA, see McGill WA
Coventry MB, see Landmark SJ
Covino BG, Marx GF, Finster M, Zsigmond EK. Prolonged sensory/motor deficits following inadvertent spinal anesthesia 1980;59:399
  see Concepcion M
  see Datta S
  see Giasi RM
  see Gissen AJ
  see Liu PL
  see Pedersen H
  see Rocco AG
  see Sage DJ
  see Sheskey MC
  Systemic toxicity of local anesthetic agents (editorial) 1978;57:387
  Vassallo HG. Local anesthetics, mechanisms of action and clinical use (book review) 1980;59:715
Covino BM, see Liu PL
Cowan GSM, see Kano T
  see Smith RH
Cowell H, see Khine HH
Cowen MJ, Bullingham RES, Paterson GMC, McQuay HJ, Turner M, Allen MC, Moore A. A controlled

Cowen MJ—*continued*
  comparison of the effects of extradural diamorphine and bupivacaine on plasma glucose and plasma cortisol in postoperative patients 1982;61:15
Cowley RA, Trump BE. Pathophysiology of shock, anoxia, and ischemia (book review) 1982;61:719
Cox BG. The author's editor (editor's choice) 1976;55:22
Cox RH, see Bagshaw RJ
Coyle DE, see Denson DD
Cozanitis DA, Heinonen J. Acute respiratory distress as a complication of left ventricular cardiac catheterization 1980;59:442
Craft JB, Jr, Co EG, Yonekura ML, Gilman RM. Nitroglycerin therapy for phenylephrine-induced hypertension in pregnant ewes 1980;59:494
  Coaldrake LA, Bolan JC, Mondino M, Mazel P, Gilman RM, Shokes LK, Woolfe WA. Placental passage and uterine effects of fentanyl 1983;62:894
  see Abboud TK
Crago BR, see Hameroff SR
Craig DB. A life-threatening complication of cricothyroid membrane puncture (case history comment) 1976;55:299
  Habib GG. Flaccid paraparesis following obstetrical epidural anesthesia: possible role of benzyl alcohol 1977;56:219
  Postoperative recovery of pulmonary function 1981;60:46
  see Pickering BG
  Ventilatory pattern, intrapleural pressure, and cardiac output (guest discussion) 1977;56:95
Crampton RS, see Lake CL
Craver JM, see Waller JL
Crawford AH, Jones CW, Perisho JA et al. Hypnosis for monitoring intraoperative spinal cord function 1976;55:42
Crawford ES, see Saleh SA
Crawford JS. Acid aspiration: recurring myths (letter) 1984;63:699
  Epidural analgesia for patients with chronic neurological disease (letter) 1983;62:620
  Epidural anesthesia for elective cesarean section (letter) 1984;63:623
  see James FM III
Crawley BE, see Dunnill RPH
Crean P, see Koren G
Creasser CW, see Stoelting RK
Crider EF. Is routine laboratory (SMA) screening justified? (correspondence) 1977;56:470
Critz A, see Hammonds W
Cromartie RS III. Rapid anesthesia induction in combat casualties with full stomachs 1976;55:74
Cronau LH, see Barash PG
Crone RK, see Goudsouzian NG
Cronnelly R, Gencarelli P, Miller RD, Fisher DM, Nguyen L. Pharmacokinetics of pancuronium and Org NC 45 (Norcuron) (abstract) 1982;61:176
  see Cahalan MK
  Morris RB, Miller RD. Comparison of thiopental and midazolam on the neuromuscular responses to succinylcholine or pancuronium in humans 1983;62:75
  Salvatierra O Jr, Feduska NJ. Renal allograft function following halothane, enflurane or isoflurane anesthesia (abstract) 1984;63:202
  see Bennett MJ
Crooks J, Stevenson IH. Drugs and the elderly (book review) 1980;59:521
Crosby IK, see Lake CL
Cross DA, Krupin T. Implications of the effects of general anesthesia on basal tear production 1977;56:35
Crowell DH, see Brower KR
Crowley TL, see Alexander GD
Crul JF, see Booij LHDJ
Crumrine ES, see Fraser JG
Cruse JM, see Lewis RE
Cryer PE, see Brown FF III
Cuasay OS, Ramamurthy R, Salem MR, Sencaydiego PM, Elgindy LI, Caburnay FS. Inorganic fluoride levels in parturients and neonates following methoxyflurane analgesia during labor and delivery 1977;56:646
Cubillos P, see Aldrete JA
Cucchiara RF. A simple technic to minimize tracheal aspiration 1976;55:816
  Blind esophageal intubation to divert gastric contents (correspondence) 1977;56:598
  see Glenski JA
  see Isenhower N
  see Mallow JE
  see Messick JM
  Wedel DJ. Finding cerebrospinal fluid during epidural blood patch: how to proceed 1984;63:1121
Cuddeback J, see Kaplan RF
Cuka DJ, Edelman JD. Atropine in physostigmine reversal of diazepam (letter) 1980;59:459
Cullen BF, Hume RB, Chretien PB. Phagocytosis during general anesthesia in man 1975;54:501
  Miller MG. Drug interactions and anesthesia: a review 1979;58:413
  see Bassell GM
  see Choi H
  see Duncan PG
  see Eyler SW
  see Miller MG
  see Pulver JJ
  see Sivarajan M
  see Tremper KK
Cullen DJ. Filters used during massive blood transfusion (questions and answers) 1975;54:45
  see Brand JB
  see Teplick R
Cullen JP, Aldrete JA, Jankovsky L, Romo-Salas F. Protective action of phenytoin in cerebral ischemia 1979;58:165
Culligan JD, see Mutch WAC
Cumming JF. The development of an acute tolerance to ketamine 1976;55:788
Cumming M, see Kozody R
Cummins DF, see Ravindran RS
  see Viegas OJ
Cunningham JG, see Sawyer DC
Curtis BM, see Scurlock JE
Curtis JD, see Hughes SC
  see Rosen MA
Curtis JP, see Abboud TK
Cuschieri A, Baker PR. Introduction to research in medical sciences (book review) 1977;56:879
Cusick JF, see Abram SE
Cwik JC. Sterilization of ampules by ethylene oxide (questions and answers) 1977;56:743
Daftarian F, see Abboud TK
Daga SR, see Shrivastava OP
Daggy BP, see Ross WT Jr
Dagnino J, see Prys-Roberts C
D'Agostino E, see Giasi RM
Dahlström B, see Rawal N
Daicoff GR, see Gordon RJ
Dailey PA, see Rosen MA
Daiz JH, Henling CE. Tension pneumoperitoneum (letter) 1982;61:624
Dajani A, see Baraka A
Dajee H, see Kapur PA
Dal Santo G. Nonrespiratory functions of the lung and anesthesia. (book review) 1978;57:383
Dalal FY, Bennett EJ, Grundy EM et al. Anesthetic considerations in diffuse bleeding diathesis of uncertain origin 1976;55:173
  see Patel KD
D'Alessandro R. *d*-Phenylalanine does not affect nocicepitive, flexion reflex thresholds in normal humans (letter) 1983;62:857
D'Allessandro FT, see Ball CG
Dalton B. A precordial ECG lead for chest operations (brief reports)

1976;55:740
Danel V, see Dupre LJ
D'Angona DS Jr, see Chernow B
Daniels AL, see Lebowitz PW
Danielson DR, see Casement BA
  see Steidl LJ
Danielson RA, see Ernst EA
Dannemiller F, see Brunner EA
Dannemiller FJ. Epidural antibiotics with prolonged catheterization (questions and answers) 1976;55:132
  see Carter GL
  see Douglas ME
  see Lunn JK
  see Sturgeon CL Jr
Danziger F, see Bernhard WN
D'Aoust B, see Deady JE
Darby R, see Dautenhahn D
Dasta JF, see Visconti JA
  Weber RJ, Wu LS, Kakos GS, Smith DF, Howie MB. Nitroglycerin pharmacokinetics in patients during cardiopulmonary bypass (abstract) 1984;63:203
Datta S, Briwa J. Modified laryngoscope for endotracheal intubation of obese patients (letter) 1981;60:120
  Brown WU Jr, Ostheimer GW, Weiss JB, Alper MH. Epidural anesthesia for cesarean section in diabetic parturients: maternal and neonatal acid-base status and bupivacaine concentration 1981;60:574
  Kitzmiller JL, Naulty JS, Ostheimer GW, Weiss JB. Acid-base status of diabetic mothers and their infants following spinal anesthesia for cesarean section 1982;61:662
  Lambert DH, Gregus J, Gissen AJ, Covino BG. Differential sensitivities of mammalian nerve fibers during pregnancy 1983;62:1070
  see Sage DJ
  see Santos A
  see Steinbrook RA
  see Warren TM
Datta TD. Flash fire hazard with eye ointment (letter) 1984;63:700
  see Ng TY
Dauchot P, Gravenstein JS. Premedication, atropine (questions and answers) 1975;54:716
Dauchot PJ, Berzina-Moettus L, Rabinovitch A, Ankeney JL. Activated coagulation and activated partial thromboplastin times in assessment and reversal of heparin-induced anticoagulation for cardiopulmonary bypass 1983;62:710
Daughters GT II, see Smith NT
Dautenhahn DL, Fagraeus L. Acid-base changes of spinal fluid during pregnancy (abstract) 1984;63:204
  Reynolds AF, Darby R, Fagraeus L. Thoracic epidural analgesia for open cordotomy 1984;63:1036
David K, see Hurlbert B
David S, see Abboud TK
Davie IT, Slawson KB, Burt RAP. A double-blind comparison of parental morphine, placebo, and oral fenoprofen in the management of postoperative pain 1982;61:1002
Davies AO. Hazards of ketamine in ischemic heart disease (letter) 1983;62:1044
Davies JM, see Strunin L
Davies KR, see Noe FE
Davies LR, see Sokol MD
Davies MJ, Liu P, Flynn MA, Liu LMP. Epidural anesthesia: 22-gauge needle 1978;57:741
Davies P, see James FM III
Davis DA, see Smith NT
Davis GC Jr, Paulsen AW, Frederickson EL. Effect of halothane and pentobarbital anesthesia on the dispersion of indicator particles passing through the central circulation of the dog 1977;56:68
Davis H. Variability of cerebrospinal fluid density (letter) 1982;61:803
Davis HS, see Bennett HL
Davis JE. Introduction of anesthesia into infant by breast feeding (questions and answers) 1977;56:744
Davis NL, de Jong RH. Successful resuscitation following massive bupivacaine overdose 1982;61:62
Davis RL, see Rosen MA
Davison JK, see Lebowitz PW
Davison R, see Harrison RA
Dawson B. Awareness, dreams, and hallucinations associated with general anesthesia (guest discussion) 1975;54:616
Day M, see O'Meara JB
Deady JE, Koblin DD, Eger EI II, D'Aoust B, Heavner JE. Anesthetic potencies and the theories of narcosis (abstract) 1980;59:535
  Koblin DD, Eger EI II, Heavner JE, D'Aoust B. Anesthetic potencies and the unitary theory of narcosis 1981;60:380
  see Koblin DD
Deane RS, see Lambert DH
De Angelis J. Clinical studies involving neostigmine reversal of *d*-tubocurarine, gallamine, and pancuronium in man (correspondence) 1975;54:118
Deas TC. Complete obstruction of an armored endotracheal tube (correspondence) 1975;54:350
  Standard nomenclature for tracheal tubes (letter) 1980;59:517
  Tracheal or endotracheal tubes? (letter) 1982;61:161
Deasi S, Roaf E, Liu P. Acute pulmonary edema during laparoscopy 1982;61:699
Deaton RL, see Ravindran RS
DeBoer GE, Kamal MM. Nitroglycerin ointment before coronary artery surgery (abstract) 1982;61:177
Debrand M, see Tsueda K
  Tsueda K, Browning SK, Wright BD, Todd EP. Anesthesia for extensive resection of congenital tracheal stenosis in an infant 1979;58:431
deBros FM, see Lebowitz PW
deBros FP, see Ramsey FM
de Bruijin NP, Stadt HH. Bilateral thrombosis of internal jugular veins after multiple percutaneous cannulations 1981;60:448
  see de Lange S
de Campo T, see Aldrete JA
De Cook TH, Goudsouzian NG. Succinylcholine drip in children—dose relationships of tachyphylaxis and phase II block development (abstract) 1980;59:535
  Goudsouzian NG. Tachyphylaxis and phase II block development during infusion of succinylcholine in children 1980;59:639
Dec-Silver H, see Smith NT
Dedrick DF, see Coté CJ
Deen SM, Marx GF. Fusion between catheter and stylet, an unusual complication of extradural analgesia 1980;59:516
Defalque RJ. Painful trigger points in surgical scars 1982;61:518
  Single-needle lateral approach for lumbar sympathetic block (correspondence) 1976;55:452
  The first experiment in obstetrical anesthesia (letter) 1983;62:1136
Dehring D, see Rosenblatt RM
de Jong RH, Bonin JC. Benzodiazepines protect mice from local anesthetic convulsions and death 1981;60:385
  Bonin JD. Deaths from local anesthetic-induced convulsions in mice 1980;59:401
  Bonin JD. Local anesthetics, injection route alters relative toxicity of bupivacaine 1980;59:925
  Deaths from local anesthetics (letter) 1980:59:955
  Local anesthetics (2nd ed). (book review) 1978;57:155
  Ronfeld RA, DeRosa RA. Cardiovascular effects of convulsant and supraconvulsant doses of amide local anesthetics 1982;61:03
  see Davis NL
  Thurman BH. Localizing the axillary

de Jong RH—*continued*
  Thurman BH—*continued*
    artery (letter) 1983;62:701
DeKornfeld TJ, Detmer MD. Medical examination review, Volume 12—Anesthesiology, 5th ed (book review) 1981;60:71
  see Finch JS
  see Israel JS
  Selected papers in respiratory therapy, second edition (book review) 1980;59:82
Delaney TJ, Kistner JR, Lake CL, Miller ED Jr. Myocardial function during halothane and enflurane anesthesia in patients with coronary artery disease 1980;59:240
  Kistner JR, Miller ED Jr, Lake CL. Cardiovascular effects of halothane and enflurane in patients with coronary artery disease (abstract) 1980;59:536
  Rowlingson JC, Carron H, Butler A. Epidural steroid effects on nerves and meninges 1980;59:610
de la Vega S, see Abouleish E
de Lange S, Boscoe MJ, Stanley TH, de Bruijin NP, Philbin DM, Coggins CH. Antidiuretic and growth hormone responses during coronary artery surgery with sufentanil-oxygen and alfentanil-oxygen anesthesia in man 1982;61:434
  see Ausems ME
  see Natua J
  Stanley TH, Boscoe M, Debuijin N, Berman L. Catecholamine and cortisol responses to high dose sufentanil-$O_2$ and alfentanil-$O_2$ anesthesia during coronary artery surgery (abstract) 1982;61:177
Delcampo C, see Moffitt EA
Delcroix C, see d'Hollander AA
Delisle S, Lebrun M, Bevan DR. Plasma cholinesterase activity and tachyphylaxis during prolonged succinylcholine infusion 1982;61:941
DelliColli P, see Ralley FE
DelPizzo A. Nonflammable germicides or detergents (correspondence) 1976;55:606
DeLuca PP, see Dorris GG
DeMarco JA, see Pan TH
Demarest RJ, see Fink RB
Demas K, see Sarnquist FH
Demers RR. Ventilatory pattern (correspondence) 1978;57:146
Demling RH, see Bodai BI
Dempsey MJ, see Farrell L
DeMunos SO, see Galindo A
Denis R, Letourneau JE, Londorf D. Reliability and validity of psychomotor tests as measures of recovery from isoflurane or enflurane anesthesia in a day-care surgery unit 1984;63:653
Denlinger JK, Nahrwold ML. Cardiac failure associated with hypocalcemia 1976;55:34
  see Alfery DD
  see Knight PR
Dennhardt R, see v. Bormann B
Dennis P, see Rosenblatt R
Dennis RG. Gag reflex (questions and answers) 1976;55:461
Denson DD, Bridenbaugh PO. Effects of epinephrine on lidocaine spinal anesthesia (letter) 1984;63:542
  Bridenbaugh PO, Phero JC, Raj PP, Turner PA, Ohlweiler DF. Evaluation of lidocaine spinal anesthesia in the rhesus monkey 1981;60:756
  Bridenbaugh PO, Turner PA, Phero JC. Comparison of neural blockade and pharmacokinetics after subarachnoid lidocaine in the rhesus monkey. II. Effects of volume, osmolality, and baricity 1983;62:995
  Bridenbaugh PO, Turner PA, Phero JC, Raj PP. Neural blockade and pharmacokinetics following subarachnoid lidocaine in the rhesus monkey. I. Effects of epinephrine 1982;61:746
  Myers JA, Thompson GA, Coyle DE. The influence of diazepam on the serum protein binding of bupivacaine at normal and acidic pH 1984;63:980
  Turner PA, Bridenbaugh PO, Thompson GA. Pharmacokinetics and neural blockade after subarachnoid lidocaine in the rhesus monkey. III. Effects of phenylephrine 1984;63:129
DePetrillo MA, see Stone JG
Depp R, see Abouleish E
de Rosayro AM, see Jones RM
Derbyshire DR. Succinylcholine-induced increases in plasma catecholamine levels in humans (letter) 1984;63:465
DerMardiosian N, see Abboud TK
Dermitzakis E, see Kaniaris P
DeRobertis M, see Moffitt EA
Derome P, see Tannieres ML
DeRosa RA  see de Jong RH
Desai PK, see Marx GF
Desai SP. Aspiration or carbon dioxide embolism? (letter) 1983;62:368
  Roaf ER. Telogen effluvium after anesthesia and surgery 1984;63:83
Desmonts JM, see d'Hollander AA
  see Duvaldestin P
Detmer MD, see DeKornfeld TJ
  see Jones RM
  see Kumar N
Deutsch S, see Bastron DR
DeVore JS. Increasing oxygenation during cesarean section (questions and answers) 1977;56:464
DeVore R, see Parker EO
  see Schwartz AJ
Dewan DM, Floyd HM, Thistlewood JM, Bogard TD. Sodium citrate premedication for elective cesarean section (abstract) 1984;63:205
  see Floyd HM
  see Kileff ME
  see Siegle JH
Dhanaraj J, see Ghoneim MM
Dhasmana KM, see van Poorten JF
d'Hollander AA, Duvaldestin P, Delcroix C, Nevelsteen M, Desmonts JM. Evolution of single twitch and train-of-four responses and of tetanic fade in relation to plasma concentrations of fazadinium in man 1982;61:225
Dhulia PN, see Sikh SS
Diamant M, Benumof JL, Saidman LJ, Kennedy J, Young P. Laparoscopic sterilization with local anesthesia: complications and blood-gas changes 1977;56:335
Diaz JH, Cooper ES, Ochsner JL. Cardiac surgery in patients with cold autoimmune diseases 1984;63:349
  Henling CE. Pneumoperitoneum and cardiac arrest during craniofacial reconstruction 1982;61:146
  see Matteo RS
  Friesen RH. Anesthetic management of congenital complete heart block in childhood 1979;58:334
Dick MM, see Kayerker UM
Dickinson GE, Myers ML, Goldbach M, Sibbald W. Acetazolamide in the treatment of ventilatory failure complicating acute metabolic alkalosis 1981;60:608
Dickson CM, see Silver DJ
Didier EP, see Haidinyak JG
Didisheim P, see Hughes DR
Diemunsch P, see Saleh-Shenaq S
Dierdorf SF, Knishna G, Anesthetic management of neonatal surgical emergencies 1981;60:204
  McNiece WL, Wolfe TM, Rao CC, Krishna G, Means LJ, Haselby KA. Effect of thiopental and succinylcholine on serum potassium concentrations in children 1984;63:1136
  see Haselby KA
  see Roesch C
DiFazio CA, Moscicki JC, Magruder MR. Anesthetic potency of nalbuphine and interaction with morphine in rats 1981;60:629

Niederlehner JR, Burney RG. The anesthetic potency of lidocaine in the rat 1976;55:818
see Burney RG
see Friedman GA
see Hecker BR
see Rowlingson JC
Difrancesco LV, see Vitez TS
Dilley RS, see Moorthy SS
Dimick AR, see Gooding JM
Dimopoulos GE, see Brock-Utne JG
Dionne RA, Goldstein DS, Wirdzek PR. Effects of diazepam premedication and epinephrine-containing local anesthetic on cardiovascular and plasma catecholamine responses to oral surgery 1984;63:640
DiPadua D, see Mathieu A
Divoll M, Greenblatt DJ, Ochs HR, Shader RI. Absolute bioavailability of oral and intramuscular diazepam: effects of age and sex 1983;62:01
Dizon CT, see Barash PG
Dmochowski J, see Young AE
Doan T, see Abboud TK
Dobkin AB, Borgstedt HH, Rohner RF et al. The influence of chronic administration of hypnotics and analgesics on rate of recovery from inhalation anesthesia in rats 1975;54:97
Development of new volatile inhalation anesthetics, (book review) 1979;58:533
Dodge TL, Mahaffey JE, Thomas JD. The anesthetic management of a patient with an obstructing intratracheal mass: a case report 1977;56:295
Dodgson BG, see Knill RL
Doershuk CF, see Lough MD
Doggart JR, see Bali IM
Dohi S, see Mayumi T
Tsuchida H, Mayumi T. Baroreflex control of heart rate during cardiac sympathectomy by epidural anesthesia in lightly anesthetized humans 1983;62:815
Doig GA, see Palahniuk RJ
Dolan EA, see Fagraeus L
Dolan PF, Shapiro S, Steinbach RB. Valve misassembly—manually operated resuscitation bag (letter) 1981;60:66
Dole KM, see Samuelson PN
Doll DC, Rosenberg H. Antagonism of neuromuscular blockage by theophylline 1979;58:139
Domaoal AM, Weniger FC, Wolfson B. "Precurarization" using pancuronium 1975;54:71
Domb GH, see Rosenblatt RM
Dominguez P, see Urzua J
Domino EF, see Pandit UA
Zsigmond EK, Domino LE, Domino KE, Kothary SP, Domino SE. Plasma levels of ketamine and two of its metabolites in surgical patients using a gas chromatographic mass fragmentographic assay 1982;61:87
Domino KB. Developments in drugs used in anaesthesia (book review) 1984;63:1052
New pharmacologic vistas in anesthesia: contemporary anesthesia practice (book review) 1984;63:964
Principles and practice of pharmacology for anaesthetists (book review) 1984;63:1145
see Bruno LA
Smith TC. Electrocautery-induced reprogramming of a pacemaker using a precordial magnet 1983;62:609
Domino KE, see Domino EF
Domino LE, see Domino EF
Domino SE, see Domino EF
Donati F, Bevan DR. Muscle electromechanical correlations during succinylcholine infusion (abstract) 1984;63:206, 1984;63:891
Bevan DR. Succinylcholine in obstetrics (letter) 1983;62:1051
Bevan DR. Twitch depression and train-of-four fade after antagonism of pancuronium with edrophonium, neostigmine, and pyridostigmine (abstract) 1982;61:178
Ferguson A, Bevan DR. Pre- and postjunctional effects of neuromuscular blocking agents and their antagonists (letter) 1983;62:1137
Twitch depression and train of four ratio after antagonism of pancuronium with edrophonium, neostigmine, or pyridostigmine 1983;62:314
Donchin M, see Berger JJ
Donegan JH. New concepts in cardiopulmonary resuscitation 1981;60:100
see Asiddao CB
Rogers MC, Traystman RJ, Koehler RC, Jones MD. Cerebrovascular response to hypoxia during barbiturate coma in lambs (abstract) 1982;61:179
The leg-heel vs the standard arm-hand method of external cardiac compression 1979;58:170
Donegan MF, see Friedman GA
Dongre SS, McAslan TC, Shin B. Selection of the source of mixed venous blood samples in severely traumatized patients 1977;56:527
Donlon JV, see McGoldrick KE
Donlon JV Jr, Savarese JJ, Ali HH. Cumulative dose-response curves for gallamine: effect of altered resting thumb tension and mode of stimulation 1979;58:377
Doolas A, see El-Baz N
Dooley JC, see Yang JC
Dorey FJ, see Conner JT
Dornette WHL. Physician-patient relationship, legal aspects of anesthesia (questions and answers) 1976;55;0643
Dorris GG, Bivins BA, Rapp RP, Weiss DL, DeLuca PP, Ravin MB. Inflammatory potential of foreign particulates in parenteral drugs 1977;56:422
Dorsch JA, Dorsch SE. Swallowing an endotracheal tube (letter) 1979;58:156
Dorsch SE, see Dorsch JA
Dorsey LM, see Kates RA
Doto JB, see Seltzer JL
Dougal RM, see Schwartz AJ
Douglas JS, see Waller JL
Douglas ME, Downs JB. Cardiopulmonary effects of PEEP and CPAP (special correspondence) 1978;57:347
Downs JB, Dannemiller FJ et al. Change in pulmonary venous admixture with varying inspired oxygen 1976;55:688
see Downs JG
see Sturgeon CL Jr
Downes H, Hirshman CA. Lidocaine aerosols do not prevent allergic bronchoconstriction 1981;60:28
Downing JW, see Brock-Utne JG
see Winning TJ
Williams V, Haschke R, Porte D, Woods S, Fogel K, Horn J. Rostal spread of epidural morphine (letter) 1984;63:375
Downing TP, see Mihm FG
Downs JB, Douglas ME, Sanfelippo PM, Stanford W, Hodges MR. Ventilatory pattern, intrapleural pressure, and cardiac output 1977;56:88
Effect of mechanical ventilation with end-inspiratory pause on blood-gas exchange (guest discussion) 1976;55:130
see Carter GL
see Douglas ME
see Stone DR
see Sturgeon CL Jr
see Wright FG Jr
Downs NH, see Graves CL
Doyle E, see Grundy BL
Drain CB, Campman KL. Drug-drug interactions in general anesthesia (editor's choice) 1975;54:76
Shipley SB. The recovery room (book

Drain CB—*continued*
  Shipley SB—*continued*
  review) 1980;59:165
Draper LD, see Rosenblatt R
Dretchen KL, see Standaert FG
Drews JH. Hazardous anesthesia machine malfunction occurring after routine prevention maintenance inspection (letter) 1983;62:701
Dring G, see Bevan DR
Drinnan AJ, see Halstead CL
Dripps RD, Eckenhoff JE, Vandam LD. Introduction to anesthesia: principles of safe practice (5th ed) (book review) 1978;57:155
Driscoll EJ, see Gelfman SS
Driscoll JJ, see Batra M
Drossou Fr, see Balamoutsos NG
Drouilhet JH, see Presbitero JV
Drummond GB. More on calculation of mean pH values (letter) 1979;58:63
  Respiratory system terminology (letter) 1983;62:862
  see Philbin DM
Drummond J, Brebner J. Physostigmine reversal of halothane anesthesia (correspondence) 1978;57:597
Dryden GE, Albrecht WH, Cummins DF, Link WJ. A nonhypoxemic system for sterile tracheal aspiration without gloves 1977;56:449
  Brickler J. Stopcock contamination 1979;58:141
  Circulatory collapse after pneumonectomy (an unusual complication from the use of a Carlens catheter): a case report 1977;56:451
  More about intubation of patients with full stomachs (correspondence) 1978;57:144
  see Ravindran RS
D'Souza J, see Bevan DR
Duarte I, see Gold MI
Dubelman AM, Forbes AR. Does cough increase the spread of subarachnoid anesthesia? 1979;58:306
Dubernet J, see Urzua J
Dubick MN, see Tsueda K
  Wright BD. Comparison of laryngeal pathology following long-term oral and nasal endotracheal intubation 1978;57:663
Dubner R, see Gracely RH
Dubois MY, Sato S, Chassy J, Macnamara TE. Effects of enflurane on brainstem auditory evoked responses in humans 1982;61:968
  see Lee VC
Dubovsky SL, Trustman R. Absence of recall after general anesthesia: implications for theory and practice 1976;55:696
Dudley H. Presentation of original work in medicine and biology (book review) 1978;57:154
Dudziak R, see Latasch L
Duff TA, see Ball CG
Dujovne CA. Cellular concentrations and toxicity of anesthetics (letter) 1979;58:259
  see Salhab AS
Dunbar BS. Drugs of choice (book review) 1983;62:243
Dunbar RW. Case history number 94: the treatment of chronic pain: a multi-faceted approach (comment) 1977;56:119
  Inflammatory potential of foreign particulates in parenteral drugs (guest discussion) 1977;56:427
  Potential clinical uses of short-acting nondepolarizing neuromuscular-blocking agents as predicted from animal experiments (guest discussion) 1975;54:677
  see Guffin AV
  see Kaplan JA
  see Kaplan JW
  "Torr," origin of the word (questions and answers) 1976;55:131
  Vasodilator treatment of heart failure after cardiopulmonary bypass (case history comment) 1975;54:842
Duncalf D. Adverse effects of increased succinylcholine doses following *d*-tubocurarine pretreatment (guest discussion) 1975;54:288
  Nagashima H, Duncalf RM. Naloxone fails to antagonize thiopental anesthesia 1978;57:558
  see Brockman E
  see El-Gaweet EI
  see Foldes FF
  see Kaplan R
  see Mogos B
  see Nagashima H
  see Radnay PA
  see Shiwaku Y
Duncalf RM, see Duncalf D
  see Shiwaku Y
Duncan GH, see Ghia JN
Duncan CJ, see Oxdil T
Duncan PG, Cullen BF, Pearsall NN. Anesthesia and the modification of response to infection in mice 1976;55:776
Dundee JD, see Johnston JR
Dundee JW. Intravenous anesthetic agents, current topics in anaesthesia, Volume 1 (book review) 1980;59:227
  Johnston JR, Moore J, McCaughey W. Use of cimetidine as an oral antacid in obstetric anesthesia (abstract) 1981;60:246
  Kawar P, Reves JG, Samuelson PN, Vinik HR. Consistency of action of midazolam (letter) 1982;61:544
  see Bali IM
  see Mirakhur RKJ
  see Mirakhur RW
Dunlop BJ, Rockoff MA, Gilroy BA, Shapiro HM. Relationship of seizure activity to neurologic outcome following cardiac arrest in the cat (abstract) 1980;59:537
  see Marsh ML
Dunn GL, see Morison DH
Dunn R, see Colley PS
Dunnill RPH, Colvin MP, Crawley DE. Clinical and resuscitative data, second edition (book review) 1980;59:463
Dunsmore RH, see Silver DJ
Dunwiddie WC, see Rah KH
Dupre LJ, Danel V, Legrand JJ, Stieglitz P. Surface landmarks for supraclavicular block of the brachial plexus 1982;61:28
Dupuis JE, see Lichtiger B
Durant PAC, see Bromage PR
  see Camporesi EM
Durkin MA, Eltringham RJ, Simpson PJ. Isosorbide dinitrate. An alternative agent to induce hypotension? (abstract) 1984;63:207
Durrani Z, see Winnie AP
Duvaldestin P, Mazze RI, Nivoche Y, Desmonts JM. Can the extent of halothane debromination be predicted preoperatively? 1979;58:470
  Mazze RI, Nivoche Y, Desmonts JM. Enzyme induction following surgery with halothane and neurolept anesthesia 1981;60:319
  see d'Hollander AA
Dwarakanath R, see Paspa P
Dworkin SF, Chen ACN, LeResche L, Clark DW. Cognitive reversal of expected nitrous oxide analgesia for acute pain 1983;62:1073
Dybbs A, see Grundy BL
Dye A, see Cartwright P
Dykes MHM, see Ovassapian A
Eagle T, see Cordes RA
Earl S, see Abboud TK
East TD, see Pace NL
Ebert PA, see Roizen MF
Ebert TJ, see Kotrly KJ
Echiverri E, see Bishay EG
Eckenhoff JE. 1978 Yearbook of anesthesia (book review) 1979;58:69
  1980 Year book of anesthesia (book review) 1981;60:233
  Bart AJ, Brunner EA, Holley HS, Linde HW. 1979 Year book of anesthesia (book review) 1980;59:319
  Controversy in anesthesiology (book review) 1980;59:316
  Health science education: responsibilities and leadership 1981;60:658
  see Dripps RD

Ecoffey C, see Benhamou D
Edde RR, Deutsch S. Cardiac arrest after interscalene brachial-plexus block 1977;56:446
  Smalley S. Defect in oxygenation associated with mannitol 1979;58:145
Edds SP, see Manchikanti L
Edelman JD, Hurlbert BJ. Intermittent left bundle branch block during anesthesia 1980;59:628
  see Cuka DJ
  see Hurlbert BJ
  see O'Gara JP
Edelstein G, see Hirshman CA
  see Marshall G
Edström H, see Santos A
  see Sheskey MC
Edwards D, see Harris JA
Edwards MW Jr, see Martin DE
Edwards R, Winnie AP, Ramamurthy S. Acute hypocapneic hypokalemia: an iatrogenic anesthetic complication 1977;56:786
Edwards RP, see Booij LHDJ
Effron DM. Cardiopulmonary resuscitation CPR (book review) 1979;58:354
Egbert B, see Baden JM
Eger EI II, Calverley RK, Smith NT. Changes in blood chemistries following prolonged enflurane anesthesia 1976;55:547
  Cardiovascular responses to nitrous oxide during light, moderate, and deep halothane anesthesia in man (guest discussion) 1978;57:93
  Cellular concentrations and toxicity of anesthetics (letter) 1979;58:259
  Isoflurane (book review) 1981;60:773
  Johnston BH. Do volatile anesthetics act as ideal gases? 1979;58:322
  Koblin DD, Collins PA. Dioxychlorane: a challenge to the correlation of anesthetic potency and lipid solubility 1981;60:211
  see Boheler J
  see Cahalan MK
  see Calverley RK
  see Cook TL
  see Deady JE
  see Eisenkraft JB
  see Fassoulaki A
  see Forbes AR
  see Gibbons RT
  see Harper MH
  see Hornbein TF
  see Horrigan RW
  see Johnson BH
  see Johnston RR
  see Kent DW
  see Koblin DD
  see Lerman J
  see McLaughlin DF
  see Munson ES
  see Shingu K
  see Smith RA
  see Steffey EP
  see Tanifuji Y
  see Way WL
  see White AE
  Shingu K, Johnson BH. Hypoxia and halothane hepatotoxicity (letter) 1983;62:861
  Toxicity of inhalation anesthetics (correspondence) 1978;57:596
  White AE, Brown CL, Biava CG, Corbett TH, Stevens WC. A test of the carcinogenicity of enflurane, isoflurane, halothane, methoxyflurane, and nitrous oxide in mice 1978;57:678
Eger RR, see Fassoulaki A
Eggers GWN Jr, see Cohen HB
Ehrenpreis MB, Oliverio RM Jr. Endotracheal tube obstruction secondary to oral preoperative medication 1984;63:867
Ehrenwerth J, see Weissman DB
Eibel P. Write to inform, not to impress (correspondence) 1976;55:895
Eie KF, see Budassi SA
Eimerl D, see Perel A
Eisele JH, Wright R, Rogge P. Newborn and maternal fentanyl levels at cesarean section (abstract) 1982;61:179
  see Lunn JK
Eisele V, Weinreich A, Bartle S. Perioperative awareness and recall 1976;55:513
Eisenberg L, see Taub HA
Eisenberg M, Balsley S, Katz RL. Effects of diazepam on succinylcholine-induced myalgia, potassium increase, creatine phosphokinase elevation, and relaxation 1979;58:314
Eisenkraft JB, Eger EI II. Nitrous oxide and Swan-Ganz catheters (letter) 1982;61:308
Eisenman TS, see Holley HS
Eisner M, see Chalon J
Elam JO. Volumetric system for monitoring minimal respiration in man 1975;54:232
El-Baz NMI, El-Ganzouri A, Gottschalk W, Jensik R. One-lung high-frequency positive pressure ventilation for sleeve pneumonectomy: an alternative technique 1981;60:683
  Braverman B, McCarthy R. Continuous jet insufflation combined with IPPV for treatment of induced ARDS: a new technique (abstract) 1984;63:208
  El-Ganzouri A, Ivankovich AD, Faber LP, Kittle CF, Jensik R. One-lung high-frequency positive-pressure ventilation during lung surgery (abstract) 1982;61:180
  Faber LP, Doolas A. Combined high-frequency ventilation for management of terminal respiratory failure: a new technique 1983;62:39
  Faber LP, Jensik RJ. Continuous epidural infusion of morphine for treatment of pain after thoracic surgery: a new technique 1984;63:757
  Holinger L, El-Ganzouri A, Gottschalk W, Ivankovich AD. High-frequency positive-pressure ventilation for tracheal reconstruction supported by tracheal T-tube 1982;61:796
El-Etr AA, see Glisson SN
  see Gorski DW
  see Ivankovich AD
  see Janeczko GF
  see Rao TLK
El-Ganzouri A, see El-Baz NMI
El-Gaweet EI, Radnay PA, Hollinger I, Duncalf D. Attentuation of hypertension and tachycardia following laryngoscopy and endotracheal intubation (abstract) 1984;63:209
Elgindy LI, see Cuasay OS
Ellis FR. Inherited disease and anaesthesia, Volume 9 (book review) 1982;61:165
Ellis RA, see Merritt JC
Ellison N, Schwartz AJ, Jobes DR, Greenhow DE, Stephenson LW. Avoidance of carotid artery puncture sequelae during internal jugular cannulation (abstract) 1982;61:181
  see Meranze J
  see Palermo LM
  see Schwartz AJ
El-Naggar M. Jet ventilation for microlaryngoscopic procedures: a further simplified technic (correspondence) 1975;54:345
  Letcher J, Middleton E, Levine H. Administration of ketamine or Innovar by the microdrip technic: a double blind study 1977;56:279
  Sadagopan S, Levine H. Factors influencing choice between tracheostomy and prolonged translaryngeal intubation in acute respiratory failure: a prospective study 1976;55:195
Elsten JL, Kim YD, Hanowell ST, Macnamara TE. Prolonged induction with exaggerated chamber enlargement in Ebstein's anomaly 1981;60:909
Eltringham RJ, see Durkin MA
Elwyn RA. Cerebrospinal fluid pressure during $O_2$ encephalography and $N_2O$ inhalation (guest discussion)

Elwyn RA—*continued* 1976;55:851
  Ring WH, Loeser E et al. Nitrous oxide encephalography: 5-year experience with 475 pediatric patients 1976;55:402
  see Ring WH
Ely SW, see Sawyer DC
Embro WJ, see Munson ES
Emerson CW, see Landry LD
Endler GC, see Garde JF
Engelhardt RC, see Vaughan RW
Engle JS, see Hecker BR
Engleman DR, see Carlson DW
English JB, see Hill GE
  see Kawamura R
Epstein BS, see McGill WA
Epstein CM, see Murkin JM
Epstein HM, Fagman W, Bruce DL et al. Intraocular pressure changes during anesthesia for electroshock therapy 1975;54:479
  Jarzemsky D, Zuckerman L, Vagher P. Plasma cholinesterase activity in bank blood 1980;59:211
  see Vender JS
Epstein RH, see Kopman AF
Epstein RM. Is your vaporizer off? (guest discussion) 1977;56:798
Erbguth PH, see Waltemath CL
Erdemir H, see Gelman S
Erdmann W, see van Poorten JF
Erickson HH, see Ritzman JR
Ericson A, Kallen B. Survey of infants born in 1973 or 1975 to Swedish women working in operating rooms during their pregnancies 1979;58:302
Eriksen S, see Sørensen O
Eriksson E. Illustrated handbook in local anaesthesia (book review) 1980;59:398
Eriksson IA, see Borg U
  Sjöstrand U. Effects of high-frequency positive-pressure ventilation (HFPPV) and general anesthesia on intrapulmonary gas distribution in patients undergoing diagnostic bronchoscopy 1980;59:585
  The role of conducting airways in gas exchange during high-frequency ventilation—a clinical and theoretical analysis 1982;61:483
  see Sjöstrand UF
Erkkola R, see Murad SHN
Erkola O, Salmenperä M, Tammisto T. Does diazepam pretreatment prevent succinylcholine-induced fasciculations? 1980;59:932
Ernst EA, Hoppel CL, Lorig JL, Danielson RA. Operating room scheduling by computer 1977;56:831
  see Lowe HJ
Ernst FW. (correspondence) 1975;54:825
  Regional anesthesia in children (guest discussion) 1975;54:389
Escarpa A, Gomez-Arnau J. Internal jugular vein catheterization; time required with several techniques under different clinical situations 1983;62:97
Eskelson CD, Hameroff SR, Kanel JS. Ethanol increases serum $\beta$-endorphin levels in rats (abstract) 1980;59:537
  see Calkins JM
Estafanous FG, see Zurick AM
  Urzua J, Zurick AM, Loop FD, Tarazi RC. Hemodynamic patterns of coronary artery surgery—role of systemic vascular resistance (abstract) 1982;61:181
  Viljoen JF, Barsoum KN. Diagnosis of pneumothorax complicating mechanical ventilation 1975;54:730
Estilo AE, Cottrell JE. Hemodynamic and catecholamine response to intravenous naloxone (abstract) 1982;61:182, 1982;61:349
Etchia A, Momnet Y. Electromechanical skin burn after transcutaneous electronerve analgesia (letter) 1982;61:801
Ethridge HC, see Solanki DR
Evans P, see Bullingham R
Everett GB, see Sivarajan M
Everts E, see Hirshman CA
Ewart RBL, Rusy BF, Bradford MW. Effects of enflurane on release of insulin by pancreatic islets in vitro 1981;60:878
Ewing BC, see Aukburg SJ
Eyler SW, Cullen BF, Murphy ME, Welch WD. Antacid aspiration in rabbits: a comparison of Mylanta and Bicitra 1982;61:288
  Cullen BF, Welch WD, Murphy M. Antacid aspiration in rabbits (abstract) 1982;61:183
Eyring H, see Ueda I
Faber LP, see El-Baz NMI
Fabian LW, see Krechel SLW
Fagman W, see Epstein HM
Fagraeus L, Angelillo JC, Dolan EA. A serious hazard during orthognathic surgery 1980;59:150
  see Christian CM
  see Dautenhahn D
Fahmy NR. Consumption of vitamin $B_{12}$ during nitroprusside administration (abstract) 1980;59:538
  Sunder N, Roberts JT. Nalbuphine: hemodynamic effects and efficacy in suppressing reflex activity in 'balanced' anesthesia (abstract) 1982;61:184
  Sunder N, Soter NA. A comparison of histamine-releasing properties and hemodynamic effects of morphine and nalbuphine in humans (abstract) 1984;63:210
Fairchild MD, see Bassell GM
Fairfax CA, see Tanz RD
Fairley HB, see Loarie DJ
  see Mulroy MF II
Fajardo L, see Glisson SN
Faltas AN, see Stone JG
Fanning GL. What route of administration for $K^+$ solutions? (correspondence) 1976;55:895
Farese G, see Gabel RA
  see Smith BE
Fargas-Babjak AM, see Morison DH
Farley WJ, Talbott GD. Anesthesiology and addiction (editorial) 1983;62:465
Farrell L, Dempsey MJ, Waud BE, Waud DR. Temperature and potency of *d*-tubocurarine and pancuronium in vitro 1981;60:18
  see Waud BE
Farzan S. A concise handbook of respiratory diseases, (book review) 1979;58:65
Fassoulaki A. Brachial plexus block for pain relief after modified radical mastectomy 1982;61:986
  Eger EI II, Johnson BH, Ferrell LD, Smuckler EA, Cahalan MK, Eger RR, Harper MH. Isoflurane does not prevent hepatic injury produced by halothane in rats 1984;63:888
  Eger EI II, Johnson BH, Ferrell LD, Smuckler EA, Harper MH, Eger RR, Cahalan MK. Brief periods of hypoxia can produce hepatic injury in rats 1984;63:855
  Eger EI II, Johnson BH, Ferrell LD, Smuckler EA, Harper MH, Eger RR, Cahalan MK. Nitrous oxide, too, is hepatotoxic in rats 1984;63:1076
  see Kaniaris P
Faust DK, Gergis SD, Sokoll MD. Management of suspected malignant hyperpyrexia in an infant 1979;58:33
Faust RJ, Nauss LA. Post-thoracotomy intercostal block: comparison of its effects on pulmonary function with those of intramuscular meperidine 1976;55:542
  see Hughes DR
  see Messick JM
Fay ML, Holzman RS. Isoflurane for resection of pheochromocytomas (letter) 1983;62:955
Feduska NJ, see Cronnelly R
Feeley TW, see Halperin BD
  see Mihm FG
Fehr BL, see Brandom BW

  see Cook DR
Fein AB, see Dobkin AB
Feingold A. Crystalloid hemodilution, hypothermia, and halothane blood solubility during cardiopulmonary bypass 1977;56:622
  Estimation of anesthetic solubilty in blood (brief reports) 1976;55:593
  MacMahon S. Patient preference for ketamine: a case report of multiple anesthesias 1975;54:35
  see Kennedy PJ
  see Velazques JL
  Use of monitor for ketamine in radiotherapy (correspondence) 1976;55:895
Feinstein AR. On central tendency and the meaning of mean for pH values (editorial) 1979;58:01
Feinstein BSH, see Bedford RF
Feldman HS, see Liu PL
  see Sage DJ
  see Welch GW
Felts JA, see Brown FF III
  see McLeskey CH
Fencl V, see Spaepen MS
  see Young AE
Fenton MV, see Hercules PR
Ferguson A, see Donati F
Ferguson TB, see Kopman EA
Feria M, see Gonzalez-Miranda F
Fermon C, see Oliverio R Jr
Ferrari AA, see Seifen AB
Ferrell LD, see Fassoulaki A
Ferrer-Brechner T. Ketamine and epilepsy (correspondence) 1976;55:446
  Winter J. Anesthetic considerations for cerebral computer tomography 1977;56:344
Ferres CJ, see Mirakhur RK
  see Pandit SK
Ferretti AM, see Sage DJ
Ferstandig LL. Trace concentrations of anesthetic gases: a critical review of their disease potential 1978;57:328
Fibuch EE, Cecil WT, Reed WA. Methemoglobinemia associated with organic nitrate therapy 1979;58:521
  Touhy GF. Intracardiac knotting of a flow-directed balloon-tipped catheter 1980;59:217
Fiddian-Green R, see Jones RM
Field JM, see Shenoy PN
Figallo EM, see McKenzie R
Fillmore RB, Herren AL, Pirlo AF. Curare sensitivity in myasthenia gravis (correspondence) 1978;57:515
Finberg JPM, see Markiewicz W
Finch JS, DeKornfeld TJ. Respiratory care case studies (book review) 1977;56:171
Finck AJ, see Kripke BJ
Finestone SC, see Ghanooni S
Fink BR. Authorship of articles in the anesthetic literature (letter) 1984;63:374
  Endotracheal tubes (questions and answers) 1975;54:715
  Gag reflex (questions and answers) 1976;55:462
  Molecular mechanisms of anesthesia: progress in anesthesiology, Volume 2 (book review) 1981;60:366
  Safety of nerve transmission (letter) 1983;62:124
  see Barsa JE
  see Bishop MJ
  see Buckley FP
  see Ogawa S
Finlayson DC. Intraoperative hemodialysis 1984;63:170
  see Brooks JL Jr
Finster M, see Covino BG
  see Pedersen H
  see Santos A
Fiolet JWT, see Bovill JG
  see Sebel PS
Firestone S, see Coté CJ
Fischbach DP, Fogdall RP. Coagulation: the essentials (book review) 1982;61:397
Fischer CG, see Binda RE
  see Cook DR
Fischer KJ. Der Einfluss von Anaesthetica auf die Kontraktionsdynamik des Herzens (book review) 1980;59:462
Fischer ND, see Carden E
Fischgrund GK, see Chalon J
  see Paspa P
Fiserova-Bergerova V. Inhibitory effect of isoflurane upon oxidative metabolism of halothane 1984;63:399
  see Holaday DA
Fisher DM, see Cronnelly R
Fisher J, see Steinbrook RA
Fisher M. Allergic response to neuromuscular relaxants (letter) 1984;63:88
Fisher MMcD, Munro I. Life-threatening anaphylactoid reactions to muscle relaxants 1983;62:559
Fishman AP. Assessment of pulmonary function (book review) 1980;59:635
Fisk GC, see Brown TCK
Fitzgerald RS, Gautier H, Lahiri S. The regulation of respiration during sleep and anesthesia, (book review) 1979;58:65
Flacke JW, Flacke WE, Bloor BC, Olewine S. Effects of fentanyl, naloxone, and clonidine on hemodynamics and plasma catecholamine levels in dogs 1983;62:305
  Flacke WE, Cant JW. Reflex responses to sodium nitroprusside and their control by cryptenamine 1980:59:909
  Flacke WE, Williams GD, Lawson NW. Control of hypertension during cardiopulmonary bypass with cryptenamine 1978;57:54
Flacke WE, see Bloor BC
  see Flacke JW
  see Fukunaga AF
  see Kapur PA
Flashberg MH. Inhalation anesthesia for coronary revascularization (letter) 1983;62:1047
  see Kopman AF
Fleisher M, see Howland
Fleming RA, see Fukui Y
  see Smith NT
Fletcher JR, see Chernow B
Fletcher R, see Nördstrom L
Flewellen EH. Burkitt's lymphoma and malignant hyperthermia (letter) 1980;59:955
  Nelson TE. Halothane–succinylcholine induced masseter spasm: indicative of malignant hyperthermia susceptibility? 1984;63:693
  Nelson TE. Is theophylline, aminophylline, or caffeine (methylxanthines) contraindicated in malignant hyperthermia susceptible patients? 1983;62:115
  see Nelson TE
Flick J, see Smith NT
Floyd HM, Dewan DM, James FM III. Coincidental fetal and maternal heart block 1981;60:59
  see Dewan DM
  see Kileff ME
Floyd JB, see Ingram CT
Flynn MA, see Davies MJ
Foëx P, see Coetzee A
  see Philbin DM
Fogdall RP. Hemodynamic effects of metocurine in patients with coronary artery disease receiving propranolol (guest discussion) 1977;56:258
  see Fischbach DP
  see VanNyhuis LS
  Sodium nitroprusside for intraoperative hypertension (correspondence) 1977;56:748
Fogel K, see Downing JW
Foldes FF, Aoki T, Ono K, Duncalf D, Nagashima H. Potentiation of pancuronium, vecuronium and atracurium by *d*-tubocurarine and metocurine (abstract) 1984;63:211
  Myasthenia gravis, use of ester-type local anesthetic (questions and answers) 1975;54:506
  see Amaki Y
  see Brückner J
  see Burkett L
  see Matsuo S

Foldes FF—*continued*
  see Nagashima H
  see Radnay PA
  see Shiwaku Y
Foley MF, see Wright FG Jr
Follath F, see Ha HR
Forbat AF, Her C. Correction for gas compression in mechanical ventilators 1980;59:488
  Zarday Z. Cardiac arrest with electromechanical dissociation 1978;57:498
Forbes AR, Cohen NH, Eger EI II. Pancuronium reduces halothane requirement in man 1979;58:497
  Gamsu G. Depression of lung mucociliary clearance by thiopental and halothane 1979;58:387
  see Dubleman AM
Ford DJ, Pither C, Raj PP. Comparison of insulated and uninsulated needles for locating peripheral nerves with a peripheral nerve stimulator 1984;63:925
  Raj PP, Singh P, Watters C. Systemic effects of topical bupivacaine (abstract) 1984;63:212
  Singh P, Watters C, Raj PP. Duration and toxicity of bupivacaine for topical anesthesia of the airway in the cat 1984;63:1001
Ford EW, Morrell F, Whisler WW. Methohexital anesthesia for surgical treatment of uncontrollable epilepsy 1982;61:185, (abstract) 997
Forestner JE. Inadvertent epidural injection of thiopental (correspondence) 1976;55:119
  Raj PP. Inadvertent epidural injection of thiopental: a case report (brief reports) 1975;54:406
Forster A, Morel D, Bachmann M, Gemperle M. Respiratory depressant effects of different doses of midazolam and lack of reversal with naloxone—a double-blind randomized study 1983;62:920
Fort NF, see Yagiela JA
Fortuna A. Droperidol and spinal anesthesia (letter) 1984;63:782
  Epidural test doses (letter) 1981;60:616
Foster AH, Carlson BM. Myotoxicity of local anesthetics and regeneration of the damaged muscle fibers 1980;59:727
Foster JA, see Burney RG
Foster SL, see Bachman TE
Foster TS, see Bennett R
Fournier SE, see Reves JG
  see Tosone SR
Fowler KC, see Gelman S
Fox F, Morrow DH, Kacher EJ, Gilleland TH II. Laboratory evaluation of pressure transducer domes containing a diaphragm 1978;57:67
Fragen RJ, Avram MJ, Henthorn TK, Caldwell NJ. A pharmacokinetically designed etomidate regimen for hypnosis 1983;62:654
  Caldwell N. Acute intravenous premedication with nalbuphine 1977;56:808
  Caldwell N, Brunner WA. Clinical use of etomidate for anesthesia induction: a preliminary report 1976;55:730
  Caldwell N. Comparison of dezocine (WY 16, 225) and meperidine as postoperative analgesics 1978;57:563
  Caldwell N. Lorazepam premedication: lack of recall and relief of anxiety 1976;55:792
  see Vree TB
  Shanks CA. Neuromuscular recovery after laparoscopy 1984;63:51
Fraley DS, Lemoncelli GL, Coleman A. Severe hypertension associated with pancuronium bromide 1978;57:265
Franatovic Y, see Arguelles JE
Francis D, see Concepcion M
Francis DM, see Raemer DB
  see Rocco AG
  see Sheskey MC
Francis RM, Kwik RSH. Oral ranitidine for prophylaxis against Mendelson's syndrome 1982;61:130
Franken EA, see Moorthy SS
Frankmann DB, see Singh-Amaranath L
Franssen E, see Newman T
Frantz RA, see Stirt JA
Fraser JG, Crumrine RS, Izant RJ Jr. A preplanned treatment for malignant hyperpyrexia 1976;55:713
  Malignant hyperthermia syndrome (correspondence) 1977;56:466
  see Koski DW
Frazer BA, see Roizen MF
Frazier CA. Insect-sting kit (correspondence) 1976;55:606
Frazier WT, Paulsen AW. Safety in operation of rechargeable ECG monitor (Tektronix) (questions and answers) 1976;55:613
Freas W, see Muldoon S
Frederickson E, see Ingram C
Frederickson EL. Cardiovascular effects of enflurane and halothane on the Rhesus monkey (guest discussion) 1976;55:90
  Longnecker DE, Allen GW. Clinical investigation of a new intravenous anesthetic—etoxadrol hydrochloride (CL-1848C; U-37862A) 1976;55:335
  see Cohen JA
  see Davis GC Jr
  see Price KA
  see Sung YF
Freed B, see Wolfson B
Freeman JV, see Garcia-Bengochea F
Freilich JD, Waterman PM, Rosenthal JT. Acute hemodynamic changes during renal transplantation 1984;63:158
Freund G. Effects of acute and chronic ethanol administration on isoflurane requirement in mice (guest discussion) 1975;54:280
Freund PR, Bowdle TA, Slattery JT, Bell LE. Caudal anesthesia with lidocaine or bupivacaine: plasma local anesthetic concentration and extent of sensory spread in old and young patients 1984;63:1017
  see Bell LE
Frey R, Safar P. Disaster medicine—types and events of disasters. Organization in various disaster situations, Volume I (book review) 1980;59:635
  see Tavares BM
Freye E, Hartung E, Schenk GK. Bremazocaine: an opiate that induces sedation and analgesia without respiratory depression 1983;62:483
Friedberg BL. Safe volume for epidural blood patches (letter) 1983;62:619
Friedman BA. Fibrinogen and albumin deficiencies associated with packed red blood cell transfusions (correspondence) 1976;55:114
Friedman CP, see Levin KJ
Friedman D, see Carden E
Friedman GA, DiFazio C. Prolonged neural blockade following regional anesthesia with 2-chloroprocaine (letter) 1980;59:810
  Norfleet EA, Bedford RF. Discontinuance of nitrous oxide does not prevent tension pneumocephalus 1981;60:57
  Rowlingson JC, DiFazio CA, Donegan MF. Evaluation of the analgesic effect and urinary excretion of systemic bupivacaine in man 1982;61:23
Friedman S, see Ramanathan S
Friesen RH, Lichtor JL. Cardiovascular depression during halothane anesthesia in infants: a study of three induction techniques 1982;61:42
  Lichtor JL. Cardiovascular effects of inhalation induction with isoflurane in infants 1983;62:411
  Lichtor JL. Indirect measurement of blood pressure in neonates and infants utilizing an automatic noninvasive oscillometric monitor 1981;60:742
  see Diaz JH
  see Myerberg DZ
Frijimori M, see Tatekawa S

Froese AB, Bryan AC. Gas exchange and high frequency ventilation (letter) 1981;60:363
  see Butler WJ
  see Kolton M
  see Rose DK
Fromme GA, see Steidl LJ
Frost EAM. Brain preservation 1981;60:821
  Outpatient evaluation: a new role for the anesthesiologist 1976;55:307
  see Levine R
  Tabaddor K, Kim BY. Induced barbiturate coma: results in 20 cases (abstract) 1981;60:247
Frumin MJ. Endotracheal tubes (questions and answers) 1975;54:715
Frutkin D, see Bloor BC
Fuchs E, see Hirshman CA
Fujimori M, see Yukioka H
Fujioka H, see Shimoji K
Fujita T, Kittani Y, Nakamura T, Kimura T. Effect of chemical sympathectomy on muscle blood flow 1977;56:653
Fukuda M, see Yamamura T
Fukuda S, Murakawa T, Takeshita H, Toda N. Direct effects of ketamine on isolated canine cerebral and mesenteric arteries 1983;62:553
  Tsuji T, Murakawa T, Takeshita H, Toda N. Effects of mepivacaine on adrenergic neuroeffector junction of the isolated rabbit aorta 1982;61:756
Fukui Y, see Smith NT
  Smith NT, Fleming RA. Digital and sampled-data control of arterial blood pressure during halothane anesthesia 1982;61:1010
Fukumasu H, see Wong KC
Fukunaga AF, Flacke WE, Bloor BC. Hypotensive effects of adenosine and adenosine triphosphate compared with sodium nitroprusside 1982;61:273
  Hung JH, Bloor BC, Sodeyama O, Olewine SK, VanEtten AP. ATP induced prolonged arterial hypotension in the anesthetized dog (abstract) 1984;63:213
  see Bishay EG
Fuleihan SF, Wilson RS, Pontoppidan H. Effect of mechanical ventilation with end-inspiratory pause on blood-gas exchange 1976;55:122
Fung DL, Liu PWW. Computer-generated pediatric data sheets for use in the operating room 1981;60:356
Funk B, see Ha HR
Funk D, Raymon F. Rheumatoid arthritis of the cricoarytenoid joints: an airway hazard 1975;54:742
Funk DI, see Shanks CA
Furman EB, see Morray JP
Furman WR, Summer WR, Sylvester JT. Relative effects of dobutamine, dopamine, and isoproterenol upon hypoxic pulmonary vasoconstriction in the pig (abstract) 1981;60:247
Furukawa K, see Yamamura T
Fusciardi J, see Benhamou D
Fyhrquist F, see Lehtinen AM
Fyman PN, Hartung J, Weinberg S, Stackhouse J. Prevalence of hepatitis B markers in the anesthesia staff of a large inner-city hospital 1984;63:433
  Schneider A, Keaney AE, Abrams LM, Casthely PA, Weinberg S. Hemodynamic effects of metubine during isoflurane anesthesia (abstract) 1984;63:214
Gabathuler ML, Kaufman RD. Respiratory depression of intravenous hydroxyzine in man: potency, duration, and lack of reversal by naloxone 1981;60:634
Gabel JC, see Bethea HL
Gabel RA. Auditing of anesthesia performance 1980;59:465
  Hooper A, Marseglia JJ Jr, Farese G. Calculation and correction of blood-gas and acid-base variables with a versatile computer program 1981;60:889
  see Raemer DB
  see Smith BE
Gadde PL, see Lees DE
Gagnon RL, see Marsh ML
  see Ward CF
Gaines GY III, see Rees DI
Gal TJ. Airway responses in normal subjects following topical anesthesia with ultrasonic aerosols of 4% lidocaine 1980;59:123
  see Rorie DK
  Suratt PM. Atropine and glycopyrrolate effects on lung mechanics in normal man 1981;60:85
  Suratt PM. Resistance to breathing in healthy subjects following endotracheal intubation under topical anesthesia 1980;59:270
  Tests of minimal obstruction in the small airways: interrelationships and physiologic significance 1977;56:242
Galdabini JJ, see Mathieu A
Galido J, see Carden E
Galindo A, Benavides O, De Munos SO, Bonilla O, Pena R. Comparision of anesthetic solutions used in lumbar and caudal peridural anesthesia 1978;57:175
  Kelly PJ. Mechanism of action of gallamine 1980;59:484
  see Gallagher TJ
  see Niejadlik K
  Witcher T. Mixtures of local anesthetics, bupivacaine-chloroprocaine 1980;59:683
Gallagher EG, see Kaplan JA
Gallagher JD, Geller EA, Moore RA, Botros SB, Jose AB, Clark DL. Hemodynamic effects of calcium chloride in adults with regurgitant valve lesions 1984;63:723
  Jose AB, Moore RA, Botros SB, Clark DL. Effects of age on extravascular lung water accumulation during coronary bypass surgery (abstract) 1984;63:215
Gallagher TJ, Banner MJ. Alternative to PEEP for maintenance of oxygenation (abstract) 1980;59:539
  Banner MJ, Barnes PA. Large-volume crystalloid resuscitation does not influence extravascular lung water (abstract) 1984;63:216
  Caruthers TE, Civetta JM. Role of micropore blood filters in respiratory failure (abstract) 1980;59:539
  Civetta JM. Acute maxillary sinusitis complicating nasotracheal intubation: a case report (brief reports) 1976;55:885
  Civetta JM. Goal-directed therapy of acute respiratory failure 1980;59:831
  Galindo A, Richey ET. Inhibition of seizure activity during enflurane anesthesia 1978;57:130
Gallant J, see Zegveld C
Galvis AG, Mestad PH. Modified endotracheal tube for airway management of children with facial burns 1981;60:116
Gambill AF, McCallum RN, Henrichs TF. Psychomotor performance following exposure to trace concentrations of inhalation anesthetics 1979;58:475
  see Cohen HB
Gamel DM, see Ward CF
Gamsu G, see Forbes AR
Gandhi S, see Ramanathan S
Gandolfi AJ, Blitt CD, Weldon S. Discoloration and impurities in isoflurane vaporizer (letter) 1983;62:366
  Brown BR. Hypoxia and halothane hepatotoxicity (letter) 1983;62:859
  see Bentley JB
  see Blitt CD
  see Borel JD
  see Soltis JJ
  see Vaughan RW
Gangat Y, see Bernstein KJ
Gans BJ, see Hoffman WE
Garber JG, Ominsky AJ, Orkin FK. Atropine in physostigmine reversal of diazepam (letter) 1980;159:459
  Ominsky AJ, Orkin FK, Quinn P. Physostigmine-atropine solution fails to reverse diazepam sedation

Garber JG—*continued*
*Ominsky AJ—continued* 1980;59:58
Garcia-Bengochea F, Munson ES. A transverse tabletop for neurosurgical operations with the patient in the lateral sitting position 1980;59:503
Munson ES, Freeman JV. The lateral sitting position for neurosurgery 1976;55:326
Garde JF, Aston R, Endler GC, Sison OS. Racial mydriatic response to belladonna premedication 1978;57:572
Gardner LB, see Sanders JH
Garg GP. Carbon dioxide retention using a humidified "nonrebreathing" system (correspondence) 1975;54:618
Garro A, see Rendell-Baker L
Garvin JP, see Warner LO
Gates SA. Gastric distension during resuscitation (letter) 1981;60:619
Gattiker RI, see Maunuksela EL
Gattinoni L, Kolobow T, Tomlinson T, Iapichino G, Samaja M, White D, Pierce J. Low-frequency positive pressure ventilation with extracorporeal carbon dioxide removal (LF PPV-ECCO$_2$R): an experimental study 1978;57:470
Gautier H, see Fitzgerald RS
Gauvin GP, see Umlas J
Gaveau T, see Rouby JJ
Gavriely N, see Bitterman H
Gay GR, Inaba DS, Rappolt RT Sr et al. "An' ho, ho, baby, take a whiff on me:" La Dama Blanca cocaine in current perspective 1976;55:582
Inaba DS. Treating acute heroin and methadone toxicity (editor's choice) 1976;55:607
Geevarghese KP, Aldrete JA, Patel TC. Inspired air temperature with immersion heater humidifiers 1976;55:331
Anesthesia for neurological surgery (book review) 1978;57:383
Geha A, see Barash PG
Geha DG, Blitt CD, Moon BJ. Prolonged neuromuscular blockade with pancuronium in the presence of acute renal failure: a case report 1976;55:343
Gehrig JD, Colpitts YH, Chapman DR. Effects of local anesthetic infiltration on brain potentials evoked by painful dental stimulation 1981;60:779
Geiger RS, Cascorbi HF. Anesthesia in an NMR scanner (letter) 1984;63:622
Gelb AW. Pseudohypotension (letter) 1982;61:713
see Kenefick JP
see Lam AM
see Lampe KM
Gelfman S, Gracely RH, Driscoll EJ, Butler D, Sweet JB, Wirdzek PR. Recovery following intravenous sedation during dental surgery performed under local anesthesia 1980;59:775
Geller EA, see Gallagher JD
see Moore RA
Gelman S, Aldrete JS, Halpern M. Hemodynamics during portacaval shunt surgery in humans (abstract) 1982;61:185
Fowler KC, Smith LR. Regional blood flow during isoflurane and halothane anesthesia 1984;63:557
Hepatic blood flow, halothane, and hypoxia (letter) 1981;60:769
Laws HL, Potzick J, Strong S, Smith L, Erdemir H. Thoracic epidural vs balanced anesthesia in morbid obesity 1980;59:948
McDowell HA, Proctor JE. Do left and right ventricular performance curves predict CVP/PAOP correlation during aortic surgery? (abstract) 1984;63:217
Reves JG, Harris D. Circulatory responses to midazolam anesthesia: emphasis on canine splanchnic circulation 1983;62:135
Rimerman V, Fowler KC, Bishop SP, Bradley EL Jr. The effect of halothane, isoflurane, and blood loss on hepatotoxicity and hepatic oxygen availability in phenobarbital-pretreated hypoxic rats 1984;63:965
see Patel K
see Shepard LS
Gemperle M, see Forster A
Gencarelli PJ, see Cronnelly R
Swen J, Koot HWJ, Miller RD. Hypocarbia and spontaneous recovery from vecuronium neuromuscular blockade in anesthetized patients 1984;63:608
Gentry S, see Stanley TH
George RB, see Light RW
George RH, see James FM III
George W, see Subaiya L
Georgiades CG, see Balamoutsos NG
Gepts E, see Camu F
Geraci CL Jr. Operating room pollution: governmental perspectives and guidelines 1977;56:775
Geraghty DM, see Cohen ML
Gerber HR, see Ha HR
Gergis SD, see Choi W
see Faust DK
see Rubbo JT
see Wanna HT
Gerlach R, see Schimek F
Gerlock AJ Jr, see Parris WCV
Gerson GR. Monitoring during anesthesia: International Anesthesiology Clinics, Volume 19, Number 11 (book review) 1981;60:846
Gerson JI, Allen FB, Seltzer JL, Parker FB Jr, Markowitz AH. Arterial and venous dilation by nitroprusside and nitroglycerin—is there a difference? 1982;61:256
Allen FB, Seltzer JL, Parker FB, Markowitz AH. Comparative arterial and venous dilation of nitroprusside and nitroglycerin (abstract) 1981;60:248
Gianaris CG. Echocardiographic analysis of human left ventricular diastolic volume and cardiac performance during halothane anesthesia 1979;58:23
Hickey RF, Bainton CR. Treatment of myocardial ischemia with halothane or nitroprusside-propranolol 1982;61:10
see Thomson IR
Gessner T, see Trudnowski RJ
Ghani GA. Fresh gas flow affects minute volume during mechanical ventilation (letter) 1984;63:619
Sung YF, Per-Lee JH. Glomus jugulare tumors—origin, pathology, and anesthetic considerations 1983;62:686
Test for a leak in the anesthesia circle (letter) 1983;62:855
Ghanooni S, Finestone SC. Inexpensive precordial stethoscope (correspondence) 1978;57:598
Wilks DH, Finestone SC. A case report of an unusual disconnection 1983;62:696
Ghia JN, Mueller RA, Duncan GH, Scott DS, Mao W. Serotonergic activity in man as a function of pain, pain mechanisms, and depression 1981;60:854
see Scott DL
see Tyler E
Ghoneim MM, Dhanaraj J, Choi WW. Comparison of four opioid analgesics as supplements to nitrous oxide anesthesia 1984;63:405
Mewaldt SP, Ambre J. Plasma levels of diazepam and mood ratings 1975;54:173
Mewaldt SP, Peterson RC. Memory effects of subanesthetic concentration of nitrous oxide (abstract) 1980;59:540
Yamada T. Etomidate: a clinical and electroencephalographic comparison with thiopental 1977;56:479
Gianaris CG, see Gerson JI
Giasi R, see Liu PL

Giasi RM, Covino BG, D'Agostino E. Pharmacokinetic interaction of local anesthetics and diazepam (abstract) 1980:59:540
Giasi RM, D'Agostino E, Covino BG. Absorption of lidocaine following subarachnoid and epidural administration 1979;58:360
Gibbons RT, Steffey EP, Eger EI II. The effect of spontaneous versus controlled ventilation on the rate of rise of alveolar halothane concentration in dogs 1977;56:32
Gibbs CP, Munson ES. Local anesthetic toxicity (letter) 1980;59:955
  see James CF
  see James CJ
Gibbs PS, LoSasso AM, Moorthy SS, Hutton CE. The anesthetic and perioperative management of a patient with documented hereditary angioneurotic edema 1977;56:571
  Moorthy SS, LoSasso AM. Sustained high inspired $PO_2$ without toxic sequelae (case history) 1976;55:588
  see Losasso AM
  see Moorthy SS
Gibson FM, see Mirakhur RK
  see Pandit SK
Gibson JR, see Gloyna DF
Gibson WC. On knowing your own history (editorial) 1979;58:04
Gier RE, see Halstead CL
Giesecke AH Jr, Beyer CW, Kallus FT. More on interpretation of pH data (correspondence) 1978;57:379
  see Samuelson RJ
Giffin JP, Cottrell JE, Hartung J, Shwiry B. Intracranial pressure during nifedipine-induced hypotension 1983;62:1078
  Cottrell JE, Shwiry B, Capuano C, O'Neill J, Hartung J. Intracranial pressure after org NC 45 (Norcuron) in cats 1984;63:218
  see Cottrell JE
Gilbert JP, see Teplick R
Gildea JE, see Lee CM
Giles R, see Barash PG
Gill K, see Cartwright P
Gill W, Long WB. Shock trauma manual (book review) 1980;59:316
Gilleland TH II, see Fox F
Gillespie TJ, see Bentley JB
Gillette JR, see Pohl LR
Gillick JS. Allergic reactions—the roles of corticosteroids, ibuprofen, $H_2$ antagonists (letter) 1983;62:857
  Spontaneous positive end-expiratory pressure (sPEEP) 1977;56:627
Gillis CN, see Cook DR
Gillman MA, Koblin DD. Nitrous oxide at analgesic concentrations—an opiate agonist: further evidence (letter) 1982;61:394
  Lichtigfeld FJ. Dual-system hypothesis of pain perception: possible further evidence (letter) 1982;61:886
Gillmor ST, see Sederberg J
  see Westenskow DR
Gilman RM, see Craft JB Jr
Gilmour IJ, see Belani KG
Gilroy BA, see Dunlop BJ
Ginsburg S, see Savarese JJ
Gintautas J, see Kraynack BJ
  see Lawson NW
Gionfriddo M, see Ali HH
  see Basta SJ
  see Goudsouzian NG
Girgis KZ, see Slogoff S
Girgis NI, see Kilpatrick ME
Girnar DS, see Thiagarajah S
  Weinreich AI. Anesthesia for transcervical thymectomy in myasthenia gravis 1976;55:13
Gisgen AJ, see Datta S
Gissen AJ, Covino BG, Gregus J. Differential sensitivity of fast and slow fibers in mammalian nerve. II. Margin of safety for nerve transmission 1982;61:561
  Covino BG, Gregus J. Differential sensitivity of fast and slow fibers in mammalian nerve. III. Effect of etidocaine and bupivacaine on fast/slow fibers 1982;61:570
  Safety of nerve transmission (letter) 1983;62:125
Giuffrida JG, Bizzarri DV. Esophageal intubation (correspondence) 1978;57:288
Glaser P, see Rouby JJ
Glass DD. Plasma heparin activity and antagonism during cardiopulmonary bypass with hypothermia (guest discussion) 1977;56:569
Glass PM, Bezzo RR. Modification of Dinamap 845 automatic blood pressure cuff to permit continuous display of cuff pressure (letter) 1982;61:476
Glasser SA. Violent fasciculations after small dose succinylcholine infusion as a first sign of atypical pseudocholinesterase 1984;63:869
Glauber DT, Buffington CW, Hornbein TF, Hamacher EN. High dose lidocaine, ultradilute epinephrine and intravenous sedation for major plastic surgery (abstract) 1984;63:219
Glauser FL, see Millen JE
Glazener EL. Introducers for 25-gauge spinal needles (letter) 1983;62:1046
  The bevel and deflection of spinal needles (letter) 1983;62:371
Glenn JJ, see Moffitt EA
Glenski JA, Cucchiara RF. Transcutaneous $O_2$ and $CO_2$ monitoring of neurosurgical patients: detection of air embolism (abstract) 1984;63:220
Glick RV. PEEP measurement (correspondence) 1978;57:144
Gliedman J, see Loeser EA
Glisson SN, Fajardo L, El-Etr AA. Amitriptyline therapy increases electrocardiographic changes during reversal of neuromuscular block 1978;57:77
  Rollo F, El-Etr AA, Bloor BC. Nitroglycerin vs sodium nitroprusside: hemodynamic and sympathoadrenal responses (abstract) 1981;60:249
  Sanchez MM, El-Etr AA, Lim RA. Nitroglycerin and the neuromuscular blockade produced by gallamine, succinylcholine, *d*-tubocurarine, and pancuronium 1980;59:117
  see Janeczko GF
Glocke MH, see Lanz E
Gloyna DF, Gibson JR. Usefulness of rapid response capnography in the detection of venous air embolism (abstract) 1984;63:221
  Huber P, Abston P, Arens JF. A comparison of blood pressure measurement techniques in the hypotensive patient (abstract) 1984;63:222
  see King WH
  see Nelson TE
Gode GR, see Kalia PK
Goetzman B, see Milstein J
Goffen BS. Transsacral block (letter) 1982;61:623
Gold MI, Duarte I, Muravchick S. Arterial oxygenation in conscious patients after 5 minutes and after 30 seconds of oxygen breathing 1981;60:313
  Muravchick S. Arterial oxygenation during laryngoscopy and intubation 1981;60:316
  Profound hypotension associated with preoperative use of phenothiazines (correspondence) 1975;54:817
  Schwam SJ, Goldberg M. Chronic obstructive pulmonary disease and respiratory complications 1983;62:975
  see Berkowitz S
  see Johnson EB
  see Levin E
  see Rodriguez R
  Treatment of bronchospasm during anesthesia 1975;54:783
Goldbach M, see Dickinson GE
Goldberg AH. The patient with heart disease: preoperative evaluation and preparation 1976;55:618
Goldberg M, see Gold MI

Goldberg ME, McSherry RT, O'Connor ME. Electrocautery and pacemaker reprogramming (letter) 1984;63:541
Goldberg RN, Platzker ACG. Organization of neonatal resuscitation equipment (letter) 1979;58:442
Goldberger E. A primer of water, electrolyte and acid-base syndromes, sixth edition (book review) 1980;59:398
Goldblatt A, see Landry LD
Goldfarb G, see Ang ET
Goldiner PL, Jain S, Rooney SM. The efficacy of transcutaneous nerve stimulation in the treatment of post-operative pain (abstract) 1980;59:541
  see Carlon GC
  see Kahn RC
  see Malloy WF
  see Rooney SM
  see Vuckovic DD
Goldman C, see Chalon J
Goldman HS, see Scarpelli EM
Goldstein DS, see Dionne RA
Goldzimer EL, Parton ME, Kane EW. Elevated intraoperative carboxyhemoglobin levels (letter) 1984;63:698
Gollan F. Effects of hemodilution on hypotension during cardiopulmonary bypass (guest discussion) 1975;54:487
Gollman D, see Whitesell R
Gomes MN, see Harnik E
Gomez QJ. The world federation of societies of anesthesiologists and you 1980;59:87
Gomez-Arnau J, see Escarpa A
Gonzales J, see Waskell L
Gonzalez-Miranda F, Juárez JB, Santos ML, Feria M. Adenosine/ATP and induced hypotension (letter) 1984;63:538
Gooding JM, Corssen G. A new introducer for percutaneous cardiovascular catheters (brief reports) 1976;55:148
  Dimick AR, Tavakoli M, Corssen G. A physiologic analysis of cardiopulmonary responses to ketamine anesthesia in noncardiac patients 1977;56:813
  Effect of etomidate on the cardiovascular system 1977;56:717
  Etomidate: an ultrashort-acting nonbarbiturate agent for anesthesia induction 1976;55:286
  Holcomb MC. Transient blindness following intravenous administration of atropine 1977;56:872
  Smith RA, Weng JT. Is methylmethacrylate safer than previously thought? (abstract) 1980;59:542
  Weng JT, Smith RA, Berninger CT, Kirby RR. Cardiovascular and pulmonary responses following etomidate induction of anesthesia in patients with demonstrated cardiac disease 1979;58:40
Goodman LI, see Moretti RJ
Gordon E. A basis and practice of neuroanesthesia, second edition (book review) 1982;61:550
  see Rudehill A
Gordon EP, Quan SF, Schlobohm RM. Hydromediastinum after placement of a thermodilution pulmonary arterial catheter 1980;59:159
Gordon G, see Amberg HL
Gordon JE, see Belani KG
Gordon RA, Ravin MB, Daicoff GR. Cardiovascular physiology for anesthesiologists, (book review) 1979;58:446
  Ravin MB, Daicoff GR et al. Effects of hemodilution on hypotension during cardiopulmonary bypass 1975;54:482
  Ravin MB. Rheology and anesthesiology 1978;57:252
Goresky G, see Koren G
Gorski DW, Rao TLK, El-Etr AA. Hemodynamic changes with enflurane, halothane, and nitroglycerin during control of intraoperative hypertension in patients with coronary artery disease (abstract) 1980;59:542
  Rao TLK. Rate of injection of protamine (letter) 1981;60:538
Gorsky BH, Gorsky SR. Introduction to medical hypnosis (book review) 1982;61:310
  Hall RL, Redford JE. Compromise for closed system anesthesia 1978;57:18
  Pain: origin and treatment (book review) 1982;61:721
Gorsky SR
  see Gorsky BH
Gory G, see Rouby JJ
Gosling CG, see Losassa AM
Goto H, Hackman LT, Arakawa K. Tracheal insertion of an esophageal stethoscope 1977;56:584
  see Ido Y
  see Kim J-M
  see Seto K
Goto Y, see Yamamura T
Gottlieb A, Lalli AF. Hypotension following contrast media injection during general anesthesia 1982;61:387
Gottschalk W. Increasing oxygenation during cesarean section (questions and answers) 1977;56:464
  see El-Baz N
Goudsouzian NG, Crone RK. Neuromuscular parameters in critically ill term and preterm infants (abstract) 1981;60:251
  Liu LMP, Coté CJ. Comparison of equipotent doses of non-depolarizing muscle relaxants in children 1981;60:862
  Liu LMP, Gionfriddo M, Otcasek D. The dose response effect of atracurium in infants (abstract) 1984;63:223
  Martyn JAJ, Liu LMP, Gionfriddo M. Safety and efficacy of vecuronium in adolescents and children 1983;62:1083
  see Coté CJ
  see De Cook TH
Gould AB Jr, see Perry LB
  see Southorn PA
Gould DB, Lampert BA, MacKrell TN. Effect of nitrous oxide solubility on vaporizer aberrance 1982;61:938
  see Lampert BA
Gould P, see Howland WS
Govier WM. Cytotoxicity of local anesthetics (letter) 1981;60:168
Gracely RH, Dubner R, McGrath PA. Fentanyl reduces the intensity of painful tooth pulp sensations: controlling for detection of active drugs 1982;61:751
  see Gelfman SS
Graedon J. The people's pharmacy: a guide to prescription drugs, home remedies, and over the counter medications (book review) 1977;56:757
Graff TD. Humidification indications and hazards in respiratory therapy 1975;54:444
Graff TE, see Alvaran SB
Graham BH, see Wilkinson PL
Graham CW, Pagano RR, Katz RL. Thrombophlebitis after intravenous diazepam—can it be prevented? 1977;56:409
  see Conner JT
  Zaccari J. Labor and delivery anesthetics decrease maternal and infant neutrophil chemotaxis (abstract) 1980;59:543
Gravenstein JS. Inadvertent epidural injection of thiopental (correspondence) 1976;55:118
  Kory WP, Marks RG. Drug abuse by anesthesia personnel 1983;62:467
  Newbower RS, Ream AK, Smith NT, Barden J. Monitoring surgical patients in the operating room (book review) 1979;58:261
  Newbower RS, Ream AK, Smith NT.

Essential noninvasive monitoring in anesthesia (book review) 1981;60:69
On criticism in medicine 1983;62:1113
see Berger JJ
see Dauchot P
see List WF
The history of drug inhalation: a brief overview 1980;59:140
Gravenstein N, van der Aa J. Mass spectrometry and the inspiratory-to-expiratory ratio (letter) 1984;63:1144
Graves CL, Downs NH, Browne AB. Cardiovascular effects of minimal analgesic quantities of Innovar fentanyl, and droperidol in man 1975;54:15
see Bidwai AV
Gravlee GP. Succinylcholine-induced hyperkalemia in a patient with Parkinson's disease 1980;59:444
Gray A, see Cartwright P
Gray DC, see Jacob LS
Gray RJ, see Moffitt EA
see Sethna DH
Gray TC, Nunn JF, Utting JE. General anaesthesia, fourth edition, Volumes 1 and 2 (book review) 1980;59:636
Graybar GB, see Kirby RR
see Youngberg JA
Green CD, Linstromberg JW. Quantification of sensory block by tetanic electrical current 1980;59:796
see Masoud PJ
Green KW. Awake endotracheal intubation (correspondence) 1976;55:120
Greenberg DJ. The incidence of aspiration in patients with tracheotomies (letter) 1984;63:1142
Greenberg LM, see Mark JB
Greenblatt DJ, see Divoll M
see Martyn JAJ
Greenblatt GM. Fiberoptic illuminating laryngoscope with remote light source—further development 1981;60:841
Greene IM. Anesthesiology and its publications 1980;59:1
Greene NM. About throwing stones from glass towers (letter) 1984;63:538
Anesthesia and the development of surgery (1846–1896) 1979;58:05
Anesthesia foundation book award 1980;59:232
Blood levels of local anesthetics during spinal and epidural anesthesia (editorial) 1979;58:357
Editor's comments 1984;63:90, 538
Evaluation of perioperative risk 1981;60:623
Further light on the potencies of local anesthetics (editorial) 1982;61:1
Gossip and the acquisition of knowledge (editorial) 1978;57:519
Middle east journal of anesthesiology (book review) 1984;63:704
Physiology of spinal anesthesia, third edition (book review) 1981;60:915
Uptake and elimination of local anesthetics during spinal anesthesia 1983;62:1013
Greenhow DE, see Ellison N
see Martin DE
see Meranze J
Greensite FS, Katz J. Spinal subdural hematoma associated with attempted epidural anesthesia and subsequent continuous spinal anesthesia 1980;59:72
Gregg JM, Campbell RL, Levin KJ et al. Cardiovascular effects of cannabinol during oral surgery 1976;55:203
Gregory GA. Respiratory failure in the child (book review) 1982;61:806
see Biehl DR
see Cameron CB
see Lerman J
see Robinson S
see Thibeault DW
Wade JG, Biehl DR, Coté J, Sitar D. Halothane MAC in the fetus (abstract) 1981;60:249
Wade JG, Biehl DR, Ong BY, Sitar DS. Fetal anesthetic requirement (MAC) for halothane 1983;62:09
Gregus J, see Datta S
see Gissen AJ
Grenvik A, Safar P. Brain failure and resuscitation (book review) 1982;61:397
Grenvik ANA. PEEP and CPAP: cardiopulmonary effects during spontaneous ventilation (guest discussion) 1977;56:639
Gresham EL. Sustained high inspired $PO_2$ without toxic sequelae (case history discussion) 1976;55:590
Graff TE, see Alvaran S
Griffen WO, see Bennett R
Griffin WO, see Tsueda K
Griffith RL III, see Rah KH
Gripenberg J, see Kalso EA
Grobler N, see Abboud T
Grodins FS, Yamashiro SM. Respiratory function of the lung and its control, (book review) 1979;58:160
Grogono AW, see Arandia HY
Kane PB. A PSRO record-keeping system for anesthesiologists 1977;56:16
see Attia RR
Gronert GA, Heffron JJA. Skeletal muscle mitochondria in porcine malignant hyperthermia: respiratory activity, calcium functions, and depression by halothane 1979;58:76
Milde JH. Variations in onset of porcine malignant hyperthermia 1981;60:499
Muscle contractures and adenosine triphosphate depletion in porcine malignant hyperthermia 1979;58:367
see Traynor CA
Susceptibility to malignant hyperthermia (letter) 1984;63:91
Thompson RL, Onofrio BM. Human malignant hyperthermia, awake episodes and correction by dantrolene 1980;59:377
Van Dyke RA. Phosphorylase activity and malignant hyperthermia (letter) 1984;63:89
Grosfeld JL, see Rao CC
Gross JB, Caldwell CB, Apfelbaum JL, Shaw LM. Effect of lidocaine infusion on the ventilatory response to hypoxia (abstract) 1984;63:224
Hartigan ML, Schaffer DW. A suitable substitute for 4% cocaine before blind nasotracheal intubation: 3% lidocaine-0.25% phenylephrine nasal spray 1984;63:915
see Hartigan ML
Smith LD, Smith TC. Ventilatory response to carbon dioxide after intravenous diazepam, (abstract) 1981;60:250
Gross S, see Chalon J
Grossberg M, see Perel A
Grossman LB, see Lee CM
Grossman RK, see Ivankovich AD
Growdon JH, see Boehm FH
Gruener R, see Blanck TJJ
Grum CM, see Vucins EJ
Grummitt RM. Balanced anesthesia does anesthetize (letter) 1984;63:1049
Grundy BL, Brown RH, Berilla JA. Fentanyl alters somatosensory cortical evoked potentials (abstract) 1980;59:544
Heros RC, Tung AS, Doyle E. Intraoperative hypoxia detected by evoked potential monitoring 1981;60:437
Jannetta PJ, Procopio PT, Doyle E, Harrison C. Somatosensory-evoked potential monitoring during neurosurgical operations (abstract) 1982;61:186
Lina A, Procopio PT, Jannetta PJ. Reversible evoked potential changes with retraction of the eighth cranial nerve 1981;60:835
Wexler DB, Spagnuolo S, Dybbs A. Effects of 10% nitrous oxide on monitoring performance and the electroencephalogram (abstract) 1980;59:545
Grundy EM, Rao LN, Winnie AP.

- Grundy EM—*continued*
  - Epidural anesthesia and the lateral position 1978;57:95
  - see Dalal FY
  - Zamora AM, Winnie AP. Comparison of spread of epidural anesthesia in pregnant and nonpregnant women 1978;57:544
- Grylack LJ, see Mendiola J
- Guenter CA, Welch MH. Pulmonary medicine (book review) 1982;61:958
- Guerra F, Aldrete JA. Emotional and psychological responses to anesthesia & surgery (book review) 1980;59:894
- Guffin AV, Dunbar RW, Kaplan JA et al. Successful use of a reduced dose of protamine after cardiopulmonary bypass 1976;55:110
  - see Kaplan JA
- Guinee WS, see Maduska AL
- Gundersen K, see Weiss R
- Gunz EF, see Stirt JA
- Gupta B, see Azar I
- Gupta CD, see Ravindram RS
  - see Ravindran RS
- Gupta RC. Epidurography: a diagnostic aid in spinal lesions (book review) 1979;58:353
- Gupta U, see Ramanathan S
- Gurmarnik S, see Rokowski WJ
- Gusdon JP, see Clark CC
- Guskiewicz RA, see Lingenfelter AL
- Gustave F, see Owens WD
- Gutsche BB, Marx GF. Spread of epidural anesthesia in pregnancy (letter) 1979;58:350
  - Missionary anesthesia (correspondence) 1975;54:819
  - Obstetric analgesia and anaesthesia (book review) 1983;62:462
  - see Johnstone RE
  - see Smith DS
  - see Zebrowski ME
- Guyton AC. An overall analysis of cardiovascular regulation, Fifteenth Annual Baxter-Travenol Lecture 1977;56:761
- Guyton R, see Kates RA
- Ha HR, Funk B, Gerber HR, Follath F. Determination of bupivacaine in plasma by high-performance liquid chromatography 1984;63:448
- Habeeb A, see Tavakoli M
- Habib GG, see Craig DB
- Habib NS, see Marx GF
- Hacker DC, see Seto K
- Hackman L, see Kim JM
- Hackman LT, see Goto H
- Hadi F, see Mackenzie CF
- Haegele KD, see Lalka D
- Haenen HTM, see Sia RL
- Hagan CH, Marshall WK, Weber DM. Effects of etomidate on brainstem auditory evoked responses (abstract) 1984;63:225
- Häggendal J see Pontén J
- Häggmark S, Nyhman Hakan, Rydvall A, Reiz S. Droperidol inhibits the effects of intravenous ketamine in patients with generalized atherosclerotic disease 1983;62:193
- Hagins FM, see Park WY
- Hahn CEW, see Adams AP
- Haid BC, see Kroesen GA
- Haidinyak JG, Didier EP. Case history number 95: anesthetics and propranolol 1977;56:283
- Hajghassemali M, see Maduska AL
- Halevy S, see Weiss RR
- Haley JV, see Morrow DH
- Hall JE, see Sudhir KG
- Hall P, see Plummer JL
- Hall RL, Cascorbi HF. Breathalyzer test and exposure to anesthetic gases (questions and answers) 1976;55:615
  - see Gorsky BH
- Halperin BD, Pearl RG, Rosenthal MH, Ashton JPA, Mihm FG, Feeley TW. Lung water following resuscitation with colloid and crystalloid solutions (abstract) 1984;63:226
- Halpern N, see Gelman S
- Halsey MJ, see Kent DW
  - see Smith RA
- Halstead CL, Blozis GG, Drinnan AJ, Gier RE. Physical evaluation of the dental patient (book review) 1982;61:890
- Halverson D, see Wilson SL
- Hamacher EN, see Glauber DT
- Hambro K, see Morita S
- Hamburg J (ed). Review of allied health education (vol 2) (book review) 1977;56:757
- Hameroff SR, Crago BR, Blitt CD, Womble J, Kanel J. Comparison of bupivacaine, etidocaine, and saline for trigger-point therapy 1981;60:752 (abstract) 1981;60:251
  - Crago BR, Cork RC, Scherer K, Leeman E. Doxepin effects on chronic pain, depression, and serum opioids (abstract) 1982;61:187
  - see Calkins JM
  - see Cork RC
  - see Eskeson CD
  - see Otto CW
  - see Reynolds AF
  - see Stiffel P
  - see Waterson CK
  - Waterson CK, Calkins JM, Robinson MS, Samoy VS. High frequency jet ventilation effects of pulse duration, frequency, and waveshape on airway pressures and $PaCO_2$ in dogs (abstract) 1981;60:252
  - Watt RC. Do anesthetics act by altering electron mobility? 1983;62:936
- Hamilton LH, see Slonim NB
- Hamilton WK. Pharmacology, pressures and people, Twelfth Annual Becton, Dickinson Lecture 1978;57:06
  - see Cahalan MK
  - see Roizen MF
  - see Wilkinson PI
- Hamm MW, see Vulliemoz Y
- Hammill M, see Tyler IL
- Hammond GL, see Barash PG
- Hammonds W, Bramwell RS, Hug CC, Najak Z, Critz A. A comparison of epidural meperidine and bupivacaine for relief of labor pain (abstract) 1982;61:187
  - Case history number 94: the treatment of chronic pain: a multi-faceted approach 1977;56:118
- Hamrick JC Jr, see Boheler J
- Hamstra R, see Sampson JF
- Hanel HK, see Viby-Mogensen J
- Hanisch EC, see Polta TA
  - see Kim YD
  - see Lee JK
- Hanowell ST, Kennedy SF. Phantom tongue pain and causalgia: case presentation and treatment 1979;58:436
  - see Elsten JL
  - see Kim YD
  - see Lee JK
- Hansen DD, see Hickey PR
- Hanson GC, Wright PL. The medical management of the critically ill (book review) 1980;59:812
- Harcus AW, Smith R, Whittle B. Pain—new perspectives in measurement and management (book review) 1978;57:751
- Hardy CA, see Sivarajan M
- Hardy JF, Morissette M, Taillefer J, Vauclair R. Pathophysiology of rupture of the pulmonary artery by pulmonary artery balloon-tipped catheters 1983;62:925
  - Taillefer J. Inflating characteristics of Swan-Ganz balloons: clinical considerations 1983;61:363
  - Taillefer J, Morrissette M. Control of pulmonary artery catheter pressures—an alternative (letter) 1984;63:467
- Harioka T, Hatano Y, Mori K, Toda N. Trimethaphan is a direct arterial vasodilator and an $\alpha$-adrenoceptor antagonist 1984;63:290
- Harkness DR. Sickling dynamics of red blood cells and other physiologic studies during anesthesia (guest discussion) 1975;54:364
- Harlan BJ, Starr A, Harwin FM. Manual

- of cardiac surgery, Volume I (book review) 1981;60:170
- Harley D, see Lippmann M
- Harlow HF. Fundamental principles for preparing psychology journal articles (editor's choice) 1976;55:455
- Harms BA, see Bodai BI
- Harnik E, Kulczycki L, Gomes MN. Transcutaneous oxygen monitoring during bronchoscopy and washout for cystic fibrosis 1983;62:357
- Haroutunian S, see Abboud TK
- Harper MH, Collins P, Johnson B, Biava CG, Eger EI II. Decrease in hepatic blood flow may cause hepatic injury during halothane anesthesia (abstract) 1981;60:253
  - Collins P, Johnson BH, Eger EI II, Biava CG. Postanesthetic hepatic injury in rats: influence of alterations in hepatic blood flow, surgery, and anesthesia time 1982;61:79
  - Eger EI II. A comparison of the efficiency of three anesthesia circle systems 1976;55:724
  - Johnson BH, Eger EI II. Celiac plexus block does not alter hepatic injury in rats 1984;63:479
  - Johnson BH, Eger EI II, Winter PM, Koblin DD. Cross tolerance between alcohol and cyclopropane in rats (abstract) 1980;59:545
  - Roizen MF. Droperidol premedication (correspondence) 1978;57:288
  - see Fassoulaki A
  - see Ingram C
  - see Shingu K
  - Winter PM, Johnson BH, Koblin DD, Eger EI II. Withdrawal convulsions in mice following nitrous oxide 1980;59:19
- Harrah JD, see Pyles ST
- Harries JD. Changing renal blood flow following sodium nitroprusside in patients undergoing nephrolithotomy (guest discussion) 1977;56:108
- Harris D, see Gelman S
- Harris JA, Biersner RJ, Edwards D, et al. Attention, learning, and personality during ketamine emergence: a pilot study 1975;54:169
- Harris PD. Medical statistics, statistical pearls I. An empty shell game 1976;55:82
  - Medical statistics, statistical pearls II. How often did that happen? 1976;55:357
  - Medical statistics, statistical pearls III. The most likely interpretation 1976;55:846
  - Statistical insights. IV. Variation as a key to research design 1978;57:322
- Harris TR, see Calkins JM
- Harris WA, see Hilgenberg JC
- Harrison C, see Grundy BL
- Harrison GG, Ivanetich K, Kaminsky L et al. Fluroxene (2,2,2-trifluroethyl vinyl ether) toxicity: a chemical aspect 1976;55:529
  - Pancuronium and the triggering of malignant hyperthermia (letter) 1980;59:889
- Harrison MJ, see Kuhnert BR
- Harrison MW, see Kingston HGG
- Harrison RA, Davison R, Shapiro BA, et al. Reassessment of the assumed A-V oxygen content difference in the shunt calculation 1975;54:198
  - see Shapiro BA
- Harsberger K, see Saleh-Shenaq S
- Harsh GR III, see McKay RD
- Hartigan ML, Cleary JL, Gross JB, Schaffer DW. Is nasal cocaine superior to a lidocaine-phenylephrine mixture for blind nasotracheal intubation? (abstract) 1984;63:227
  - see Gross JB
- Hartsfield SM, see Sawyer DC
- Hartung E, see Freye E
- Hartung J, see Cottrell JE
  - see Fyman PN
  - see Giffin JP
- Harwin FM, see Harlan BJ
- Hasbrouck JD, Coleman CC. Effect of halothane on systolic time intervals 1977;56:522
- Haschke RH, see Bashein G
  - see Downing JW
- Haselby KA, Dierdorf SF. A gravity-driven continuous flush system for vascular catheters 1982;61:871
  - McNiece WL. Respiratory obstruction from uvular edema in a pediatric patient 1983;62:1127
  - Neurofibromatosis, renal hypertension, and cardiac dysrhythmias (case history comment) 1975;54:544
  - see Dierdorf SF
  - see Roesch C
  - Wolfe T, Rao CC, Krishna G, Dierdorf SF. Effects of age upon epinephrine-induced arrhythmias during halothane anesthesia in pigs (abstract) 1981;60:254
- Hashimoto Y, see Iwatsuki N
  - Watanabe H, Satou M. Anesthetic management of a patient with hereditary fructose-1,6-diphosphatase deficiency 1978;57:503
- Haskel Y, see Vatashsky E
- Hassan SZ. Caudal anesthesia in infants 1977;56:686
  - Matz GJ, Lawrence AM et al. Laryngeal stenosis in acromegaly: a possible cause of airway difficulties associated with anesthesia 1976;55:57
  - see Meltzer HY
  - see Moretti RJ
- Hasselstrøm LJ, Mogensen T, Kehlet H, Christensen NJ. Effects of intravenous bupivacaine on cardiovascular function and plasma catecholamine levels in humans 1984;63:1053
- Hastings A, see Rafferty TD
- Hatano Y, see Harioka T
- Hatcher CR, see Kaplan JA
- Hathaway BN, Hill GE, Ohmura A. Centrally induced sympathetic dystrophy of the upper extremity 1978;57:373
- Hatt J, see Hill GE
  - see Bålfors E
- Haupt HM, see Chen CT
- Hayden J, see Jorgenson NB
- Hayes JJ Jr, see Kamaya H
- Hayes JK, see Westenskow DR
- Hazelwood J, see Lewis RE
- Heard SO, Munson ES. Ventilator alarm nonfunction associated with a scavenging system for waste gases 1983;62:230
- Heath KR, see Saltzman LS
- Heaton JA, see Maduska AL
- Heavner JE, see Deady JE
- Hecker BR, Lake CL, DiFazio CA, Moscicki JC, Engle JS. The decrease of the minimum alveolar anesthetic concentration produced by sufentanil in rats 1983;62:987
- Heerdt ME. Pollution, a cause for concern 55 years ago, too (correspondence) 1978;57:516
  - see Mazze RI
- Heffron JJA, Mitchell G. Diagnostic value of serum creatine phosphokinase activity for the porcine malignant hyperthermia syndrome 1975;54:536
  - see Gronert GA
  - see Mitchell G
- Hehre FW. Bupivacaine compared with etidocaine for vaginal delivery (guest discussion) 1975;54:255
  - see Joshi SM
- Heinecke A, see Van Aken H
- Heinonen J, see Cozanitis DA
  - see Salemenperä M
- Hekman W, see Prakash O
- Helrich M, see Lichtenfeld KM
- Hempel V, Liu PWW. Computer-generated pediatric data sheets for use in the operating room 1981;60:356
  - van Finck, Baumgärtner E. A longitudinal supraclavicular approach to the brachial plexus for the insertion of plastic cannulas 1981;60:352

Hempelmann G, see v. Bormann B
Hendershot RJ, see Cook DR
  see Jones JF
Hendler N. Diagnosis and nonsurgical management of chronic pain (book review) 1981;60:620
Hendricks PL, see McKay RD
Hendrickx HHL, Trahey GE, Argentieri MP. Paradoxical inhibition of decreases in body temperature by use of heated and humidified gases (letter) 1982;61:393
Hendrie M, see Ravindran RS
Hendriksen E, see Abboud TK
Henling CE, see Diaz JH
  Slogoff S, Kodali SV, Arlund C. Heart block after coronary artery bypass—effect of chronic administration of calcium-entry blockers and $\beta$-blockers 1984;63:515
Henning RJ, see Weil MH
Henrichs TF, see Gambill AF
Henriksen EH, see Abboud TK
Henschel EO. Malignant hyperthermia: current concepts (book review) 1978;57:153
  see Patel KD
Hensinger RN, see Waldman J
Henthorn TK, see Fragen RJ
  see Shanks CA
Hentz RV, see Merrill DG
Her C, see Forbat AJ
Hercules PR, Lekwart FJ, Fenton MV. Pulmonary restriction and obstruction, a programmed text (book review) 1980;59:896
Hermens JM, Bennett MJ, Hirshman CA. Anesthesia for laser surgery 1983;62:218
Herndon PS, see Morray JP
Herold RA, see Naulty JS
Heros RC, see Grundy BL
Herr G, see Sivarajan M
Herren AL, see Benumof JL
  see Fillmore RB
  see Mitchell SA
  see Pease RD
Hertz R, Chiovari CA, Marx GF. Delayed Horner's syndrome following obstetric extradural block 1980;59:299
Heskett T, see Tanz RD
Hess DG, see Smith BE
Hess W, Arnold B, Schulte-Sasse U, Tarnow J. Comparison of isoflurane and halothane when used to control intraoperative hypertension in patients undergoing coronary artery bypass surgery 1983;62:15
  Inhalation anesthesia for coronary revascularization (letter) 1983;62:1047
  see Schulte-Sasse U
Hetherington A, see Rosenblatt RM
Hewson JR. Calculation of alveolar oxygen tension (correspondence) 1978;57:746
  Perfusion characteristics during cardiopulmonary bypass and subsequent changes in alveolar-arterial oxygen tension gradients 1978;57:298
Heyduk J, see Stanec A
Heykants J, see Camu F
Heyman HJ, Salem MR, Klimov I. Persistent sixth cranial nerve paresis following blood patch for postdural puncture headache 1982;61:948
  see Janeczko GF
Hibbard A, see Bishop MJ
Hickey PR, Hansen DD. Fentanyl- and sufentanil-oxygen-pancuronium anesthesia for cardiac surgery in infants 1984;63:117
  Hansen DD, Norwood WI, Castaneda AR. Anesthetic complications in surgery for congenital heart disease 1984;63:657
Hickey RF, see Gerson JI
  see Hoar PF
  see Mangano DT
  see Shingu K
Hicks HC, Mowbray AG, Yhap EO. Cardiovascular effects of and catecholamine responses to high dose fentanyl-$O_2$ for induction of anesthesia in patients with ischemic coronary artery disease 1981;60:563
Hicks JN, see Patel KF
Hicks JS, Levinson G, Shnider SM. Obstetric anesthesia training centers in the U.S.A.—1975 1976;55:839
Hilgenberg JC. Comparison of the pharmacology of vecuronium and atracurium with that of other currently available muscle relaxants 1983;62:524
  McCammon RL, Harris WA. Hemodynamic effects of slow bolus administration of atracurium in vascular surgical patients (abstract) 1984;63:228
  McCammon RL, Stoelting RK. Pulmonary and systemic vascular responses to nitrous oxide in patients with mitral stenosis and pulmonary hypertension 1980;59:323 (abstract) 1980;59:546
  see McCammon RL
  see Moorthy SS
  see Stoelting RK
  Stoelting RK. Characteristics of succinylcholine-produced phase II neuromuscular blocking during enflurane, halothane, and fentanyl anesthesia 1981;60:192 (abstract) 1981;60:255
  Stoelting RK, King RD. Direct cardiac index determination using a thermodilution computer (letter) 1982;61:162
 Johantgen WC. Bradycardia after intravenous fentanyl during subarachnoid anesthesia (letter) 1980;59:162
Hill AB, see Jones RM
Hill AG, see Knight PR
Hill D, see Meuleman TR
Hill DW. Physics applied to anaesthesia (book review) 1977;56:171
  Physics applied to anesthesia, fourth edition (book review) 1981;60:172
Hill GE, English JE, Lunn J, Stanley TH, Sentker CR, Loeser EA, Liu WS, Kawamura R, Bidwai AV, Hodges M. Cardiovascular responses to nitrous oxide during light, moderate and deep halothane anesthesia in man 1978;57:84
  Lunn JK, Hodges MR, Stanley TH, Sentker CR, Johansen RK, Hatt J. $N_2O$ modification of halothane-altered renal function in the dog 1977;56:690
  see Hathaway BA
  see Kawamura R
  see Stanley TH
  see Wassill VM
  Stanley TH, Hodges MR, Sentker CR, Philbin D. Failure of enflurane in altering renal responses to acute intracranial pressure increases 1978;57:200
  Lunn JK, Liu WS, English JB, Loeser EA, Kawamura R, Sentker CR, Hill HR. Neutrophil chemotaxis during halothane and halothane-$N_2O$ anesthesia in man 1977;56:696
  Wong KC, Shaw CL, Blatnick RA. Acute and chronic changes in intra- and extracellular potassium and responses to neuromuscular blocking agents 1978;57:417
Hill HR, see Hill GE
  see Stanley TH
Hill SA, see Su JY
Hillman DE, see Chalon J
  see Wang BC
Hillyer KW, Johnston RR. Unsuspected dilution of anesthetic gases detected by an oxygen analyzer 1978;57:491
Hinsvark ON, see Weiss R
Hirshman CA, Bergman NA. Halothane and enflurane protect against bronchospasm in an asthma dog model 1978;57:629
  Leon D, Edelstein G, Brackebusch M, Casson H, Barry J, Fuchs E. Risk of

hyperkalemia in recipients of kidneys preserved with an intracellular electrolyte solution 1980;59:283
  - Leon D, Proch D, Everts E, Smith JD. Improved metal endotracheal tube for laser surgery of the airway 1980;59:789
  - see Barnett AS
  - see Bennett MJ
  - see Downes H
  - see Hermens JM
  - see Kingston HGG
  - see Marshall G
  - see Weber L
- Hitt BA, Mazze RI, Cook TL, et al. Thermoregulatory defect in rats during anesthesia 1977;56:09
  - see Cook TL
  - see White AE
- Hixon SJ, see Assmann DC
- Hoar PF, Nelson NT, Mangano DT, Bainton CR, Hickey RF. Adrenergic response to morphine-diazepam anesthesia for myocardial revascularization 1981;60:406
  - see Stone JG
- Hobbs EG, see Byrick RJ
- Hobelmann CF Jr, Smith DE, Virgilio RW. A magnetic PEEP valve 1977;56:580
- Hochman BN, see Reisner LS
- Hodges MR, see Downs JB
  - see Hill GE
  - see Kawamura R
  - see Loeser EA
  - see Stanley TH
  - see Westenskow DR
- Hodgkinson R. Anesthetic management of a parturient with severe juvenile rheumatoid arthritis 1981;60:611
  - Husain FJ. Epidural test dose in obstetrics (letter) 1980;59:811
  - Husain FJ. Intravascular migration of epidural catheters (letter) 1979;58:443
  - Husain FJ. Obesity and the cephalad spread of analgesia following epidural administration of bupivacaine for cesarean section 1980;59:89
  - Husain FJ. Obesity, gravity, and spread of epidural anesthesia 1981;60:421
  - Marx GF, Kim SS, Miclat NM. Neonatal neurobehavioral tests following vaginal delivery under ketamine, thiopental, and extradural anesthesia 1977;56:548
  - see Kim SS
  - see Miclat NN
- Hodgson BJ, see Jones DJ
- Hoeneveld MH, see Bovill JG
- Hoff BH, Robotham JL, Smith RB, Cherry D, Bunegin L. Effects of high frequency ventilation (300 to 2400/min) on cardiovascular function and gas exchange in dogs (abstract) 1981;60:256
- Hoffer L, see Reitz J
- Hoffman JC, see Munson ES
- Hoffman JF. Membrane transport processes. Vols. I and II (book review) 1978;57:384
- Hoffman S, Jedeikin R. Swallowed endotracheal tube in an adult 1984;63:457
  - see Jedeikin RJ
  - see Shapiro LA
- Hoffman WE, Satinover I, Miletich DJ, Albrecht RF, Gans BJ. Cardiovascular changes during sodium nitroprusside or adenoside triphosphate infusion in the rat 1982;61:99
- Holaday DA, Fiserova-Bergerova V. Uptake and excretion of 1-bromo-1,2,2-triflurocyclobutane (42M-9) in man: comparative study on pharmacokinetics and metabolism of inhalation anesthetics 1976;55:853
  - see Berman ML
- Holbrook GW, see Kaplan JA
  - see Welti RS
- Holbrook P, see Chernow B
- Holcomb MC, see Corssen G
  - see Gooding JM
- Holdcroft A. Body temperature control (book review) 1981;60:366
- Holinger L, see El-Baz N
- Holland D, see Coetzee A
- Holley HS, Eisenman TS. Hazards of an anesthetic scavenging device (letter) 1983;62:458
  - Operating room communication system 1983;62:454
  - see Eckenhoff JE
  - see Lichtenthal PR
- Hollinger I, see El-Gaweet EI
- Holzer JA, see Rampil IJ
- Holzman RS, see Fay ML
- Homann B, see Blumenberg D
- Homi J. Missionary anesthesia (correspondence) 1975;54:819
  - see Linde HW
- Homma E, Collins JG, Kitahata LM. Spinal morphine analgesia: possible mechanisms in cats (abstract) 1982;61:188
  - see Collins JG
  - see Kawahara M
- Hommelgaard P, see Sitorenson O
- Hondeghem L, see Clarkson CW
- Hong JC, see Sohn YZ
- Hood JB, see Cooke JE
  - Wallace CT, Mahaffey JE. Anesthetic management of an intracranial arteriovenous malformation in infancy 1977;56:236
- Hook R, see Barretto CT
- Hooks PJ, Scarberry EH, Bryan-Brown CW. The pharyngeal tracheal lumen (PTL) airway: a one-handed emergency resuscitation tube (abstract) 1984;63:229
- Hooper A, see Gabel RA
- Hooper D, see Coombs DW
- Hopkins RL. Extubation in epiglottitis (letter) 1984;63:468
- Hopkinson R, see James FM III
- Hopkinson RB, Parkin CE. Hydrohemothorax following percutaneous internal jugular vein cannulation recognized by intravenous pyelography 1978;57:507
- Hopp FA, see Palmer SK
- Hoppel CL, see Ernst EA
- Horn B. Single-needle lateral approach for lumbar sympathetic block (correspondence) 1976;55:452
- Horn J, see Downing JW
- Hornbein TF, Eger EI II, Winter PM, Smith G, Wettone D, Smith KH. The minimum alveolar concentration of nitrous oxide in man 1982;61:553
  - see Glauber DT
- Horrigan RW, Eger EI, Wilson C. Epinephrine-induced arrythmias during enflurane anesthesia in man: a nonlinear dose-response relationship and dose-dependent protection from lidocaine 1978;57:547
  - Physostigmine and anesthetic requirement for halothane in dogs 1978;57:180
  - Physostigmine reversal of halothane anesthesia (correspondence) 1978;57:598
- Horrow JC, see Bartkowski RR
  - see Metz S
- Horton WG, see Moore DC
- Hosobuchi Y, see Way WL
- Hotvedt R, Refsum H, Platou ES. Cardiac electrophysical and hemodynamic effects of $\beta$-adrenoceptor blockade and thoracic epidural analgesia in the dog 1984;63:817
- Houghton FM, see Bullard FR
- Howard DR, see Sawyer DC
- Howard PJ, see Johnston JR
- Howe JR. Patient care in neurosurgery (book review) 1977;56:881
- Howell RE, see Cook DR
- Howes J, see Schwartz AJ
- Howie MB, Lingman RP, Reilley TE, Varma AB, Lee JJ. Plasma fentanyl levels necessary for maintenance of cardiovascular stability (abstract) 1982;61:188
  - see Dasta JF
  - see Reitz J

Howland D Jr, see Steffey EP
Howland WS. Fibrinogen and albumin deficiencies associated with packed red blood cell transfusions (correspondence) 1976;55:115
  NaHCO$_3$ use with the administration of bank blood (questions and answers) 1976;55:274
  Schweizer O, Fleisher M et al. Fibrinogen and albumin deficiencies associated with packed red blood cell transfusions 1975;54:89
  see Carlon GC
  see Kahn RC
  see Underwood P
Huang KC, Kraman SS, Wright BD. Video stethoscope—a simple method for assuring continuous bilateral lung ventilation during anesthesia 1983;62:586
Hubbert CH. Covert seizures as a cause of post-operative apnea 1978;57:136
Huber P, see Priano LL
Huber PA, see Gloyna DF
  see King WH
Hudon G, see Boulanger M
Huffman JP. Indirect-direct laryngoscope (brief reports) 1975;54:404
Hufstedler SM, see Tremper KK
Hug CC Jr, see Ausems ME
  Pharmacokinetics of drugs administered intravenously (review article) 1978;57:704
  see Hammonds W
  see Kates RA
  see Moldenhauer CC
  see Murkin JM
  see Waller JL
  see Welti RS
Hugenholtz PG, see Prakash O
Hughes DG, Longan M, Ryan DW. Blue jumpers and pink trousers 1981;60:453
Hughes DR, Faust RJ, Didisheim P, Tinker HJ. Heparin monitoring during cardiopulmonary bypass in man: use of fluorogenic heparin assay to validate activated clotting time (abstract) 1982;61:189
  see Warner MA
Hughes SC, Abboud TK, Shnider SM, Stefani SJ, Norton M. Maternal and neonatal effects of epidural morphine for labor (abstract) 1982;61:190
  Rosen MA, Shnider SM, Abboud TK, Stefani SJ, Norton M. Maternal and neonatal effects of epidural morphine for labor and delivery 1984;63:319
  Rosen MA, Shnider SM, Norton M, Curtis JD. Epidural morphine for the relief of postoperative pain after cesarean section (abstract) 1982;61:190
  see Abboud TK
  see Rosen MA
Hughes T, see Carden E
Hull CJ, see Sykes MK
Hume RB, see Cullen BF
Humphrey LS, see Cork RA
Hung JH, see Fukunaga AF
Hunt JR, Rigor BM Sr, Collins JR. The potential for contamination of continuous epidural catheters 1977;56:222
Hunt PCW, Cotton BR, Smith G. Comparison of the effects of pancuronium and atracurium on the lower esophageal sphincter 1984;63:65
Hunter JW, see Margand PMS
Huntington CT, Cohn ML, Byrd SE. Combined use of epidural morphine and steroid in recurrent postsurgical low back pain syndrome (abstract) 1982;61:191
Hupert C, Yacoub M, Turgeon LR. Effect of hydroxyzine on morphine analgesia for the treatment of postoperative pain 1980;59:690
Hurlbert BJ Cohn ML, Byrd SE, Combined use of epidural morphine and steroid in recurrent postsurgical low back pain syndrome, (abstract) 1982;61:191
  Edelman JD, David K. Serum potassium levels during and after terbutaline 1981;60:723
  see Edelman JD
  see Larson GF
  see Moravec MA
  see Newland MC
Hurley EJ, see Safwat AM
Husain FJ, Marx GF. Left-sided chest pain with radiation to the shoulder after vaginal delivery 1977;56:863
  see Hodgkinson R
Huswman B, see Palm T
Hutchins GM, see Chen CT
Hutton CE, see Gibbs PS
Hwang HS see Shiau HF
Hyman AI, see Rosenbaum SH
Iapichino G, see Gattinoni L
Ido Y, Goto H, Lavin MJ, Robinson JD, Mangold JV, Arakawa K. Effects of positive end-expiratory pressure on carotid blood flow during closed-chest cardiopulmonary resuscitation in dogs 1982;61:557
Iliadelis E, see Balamoutsos NG
Imle PC, see Mackenzie CF
Imrie DD, see Moffitt EA
Inaba DS, see Gay GR
Ingels NB Jr, see Smith NT
Ingersoll I, Lell W, Allarde R et al. The role of profound hypothermia in infants undergoing surgical correction of complicated heart defects 1975;54:660
Ingram C, Frederickson E, Kutner MH, Harper MH. Inappropriateness of statistical methods used in evaluating postanesthetic hepatic injury (letter) 1982;61:718
Ingram CT, Floyd JB, Santora AH. Aortic and mitral valve replacement after sickle cell crisis (letter) 1982;61:802
Inoue K. Effects of anesthetics on central vagal tone (letter) 1984;63:371
Irarrazaval M, see Urzua J
Isaacson IJ, see Berry AJ
Isac F, Moffitt EA. Emergency operation during acute myocardial infarction (case history) 1975;54:267
Isenberg MD, see Mulroy MF II
Isenhower N, Cucchiara RF. Anesthesia for vanishing lung syndrome: report of a case 1976;55:750
Isern-Amaral J, see Liu WS
  see Stanley TH
Islander G, see Carlsson C
Israel JS, DeKornfeld TJ. Recovery room care (book review) 1982;61:719
Ito H, see Bishay EG
Ivanetich K, see Harrison GG
Ivanetich KM, Bradshaw JJ, Brittain T. Limitations of the sodium fusion assay for fluorinated metabolites 1982;61:786
  see Bradshaw JJ
Ivankovich AD. Absence of autoregulation of cerebral blood flow during halothane and enflurane anesthesia, Reply to Dr. Brunner's comments 1976;55:107
  Braverman BD, Klowden AJ, Heyman HJ. Prevention of nitroprusside toxicity with thiosulfate (abstract) 1980;59:547
  Braverman BD, Shulman M, Klowden AJ. Prevention of nitroprusside toxicity with thiosulfate in dogs 1982;61:120
  El-Etr AA, Janeczko GF et al. The effects of ketamine and of Innovar anesthesia on digitalis tolerance in dogs 1975;54:106
  Miletich DJ, Grossman RK et al. The effect of enflurane, isoflurane, fluroxene, methoxyflurane and diethyl ether anesthesia on ouabain tolerance in the dog 1976;55:360
  Nitroprusside and other short-acting hypotensive agents (book review) 1979;58:66
  see Braverman BD
  see Cairoli VJ
  see El-Baz NMI
  see Janeczko GF
  see Miletich DJ

  see Zahed B
Iwane T, Maruyama M, Matsuki M et al. Management of intractable pain in adiposis dolorosa with intravenous administration of lidocaine 1976;55:257
Iwatsuki K, see Iwatsuki N
Iwatsuki N, Covino BG, Hashimoto Y, Amaha K, Obara S, Iwatsuki K. Inotropic effects of nondepolarizing muscle relaxants in isolated canine heart muscle 1980;59:717
  Koga Y, Amaha K. Calcium channel blocker for treatment of malignant hyperthermia (letter) 1983;62:861
  Matsukawa S, Iwatsuki K. A weak negative inotropic effect of protamine sulfate upon the isolated canine heart muscle 1980;59:100
Izant RJ Jr, see Fraser JG
Izukawa I, see Steward DJ
Jablonski J, see Whitesell R
Jackson D, see Carrow DJ
Jackson PF, see Kumar SM
Jackson R, see Cohen ML
Jackson SH, Smith NT. Acetate fails to reverse myocardial depression in dogs anesthetized with halothane 1978;57:395
Jacob LS, Gray DC. Neck pain: an unusual presentation of bladder perforation 1980;59:801
Jacobs HK, see Mathru M
  see Rao TLK
Jacoby J. Laryngeal sequelae of endotracheal intubation (guest discussion) 1975;54:769
  see Seltzer JL
Jacoby RM, see Wassill VM
Jacox AK. Pain: A source book for nurses and other health care professionals (book review) 1977;56:879
Jadwat C, see Lear E
Jahn EP, see Palmer SK
Jain S, see Goldiner PL
  see Rooney SM
James CF, Gibbs CP. An evaluation of sodium citrate solutions (letter) 1983;62:241
  Modell JH, Gibbs CP, Kuck EJ, Ruiz BC. Pulmonary aspiration—effects of volume and pH in the rat 1984;63:665
James CJ, Gibbs CP. Nonparticulate antacid (letter) 1982;61:801
James DJ, Bedford RF. Hydralazine for controlled hypotension during neurosurgical operations 1982;61:1016
  Bedford RF. Hydralazine for controlled intraoperative hypotension (abstract) 1982;61:192
James FM III, Crawford JS, Hopkinson R, Davies P, Naiem H. Comparison of general anesthesia and lumbar epidural analgesia for elective cesarean section 1977;56:228
  George RH, Naiem H et al. Bacteriologic aspects of epidural analgesia 1976;55:187
  Neonatal neurobehavioral responses (letter) 1984;63:1045
  see Floyd HM
  see Kileff ME
  see Siegle JH
  Wheeler AS. Obstetric anesthesia: the complicated patient (book review) 1982;61:626
James MFM, White JF. Anesthetic considerations at moderate altitude 1984;63:1097
James OF, see Reitan JA
Jane JA, see Bedford RF
Janeczko GF, Ivankovich AD, Glisson SN, Heyman HJ, EL-Etr AA, Albrecht RF. Enflurane anesthesia for surgical removal of pheochromocytoma 1977;56:62
  see Ivankovich AD
Janis KM. Intermittent mandatory ventilation (correspondence) 1976;55:120
Jankovic D, see Lanz E
Jankovsky L, see Cullen JP
Jannetta PJ, see Grundy BL
Janowsky DS, see Janowsky EC
Janowsky EC, Janowsky DS, Pechnick R. Local anesthetic toxicity (letter) 1981;60:455
  see Archer TL
Jarboe TM, see Zwagil LW
Jarzemsky D, see Epstein HM
Jascott D, see Kahn RC
Jatlow P, Barash PG, Van Dyke C, Radding J, Byck R. Cocaine and succinylcholine sensitivity: a new caution 1979;58:235
Jeal DE. Head strap modification (letter) 1980;59:809
Jebeles JA, see Kissin I
Jedeikin R, see Hoffman S
  see Shapiro LA
Jedeikin RJ, Hoffman S. The ocular reflex in eye-surgery anesthesia 1977;56:333
Jenkins MT, see Kallus FT
  see Raj PP
Jenkins TE, see Pauca AL
Jensik RJ, see El-Baz NMI
Jeon IS, see Koka BV
Jeppsen A, see Lui WS
Jobes DR. Acute cardiovascular management—anesthesia and intensive care (book review) 1983;62:622
  see Ellison N
  see Schwartz AJ
Johans TG, Reichert TJ. An insufflation device for anesthesia during subglottic carbon dioxide laser microsurgery in children 1984;63:368
Johansen RK, see Hill GE
  see Loeser EA
Johantgen WC, see Hilgenberg JC
Johnson BH, Eger EI II. Bactericidal effects of anesthetics 1979;58:136
  see Eger EI II
  see Fassoulaki A
  see Harper MH
  see Koblin DD
  see Shingu K
  see Steffey EP
  see Way WL
Johnson CC, see Westenskow DR
Johnson EB, Gold MI. Bronchospasm during pelvic surgery: prostaglandin–kinin pathogenesis? 1983;62:104
Johnson GN, see Palahniuk RJ
Johnson J, see Abboud TK
Johnson KA, see Rorie DK
Johnson SB. Warming povidone–iodine solution for skin preparation (correspondence) 1978;57:142
Johnson SP, see Waller JL
Johnston JR, Moore J, McCaughey W, Dundee JD, Howard PJ, Toner W, McClean E. Use of cimetidine as an oral antacid in obstetric anesthesia 1983;62:720
  see Dundee JW
Johnston RR, Eger EI II, Wilson C. A comparative interaction of epinephrine with enflurane, isoflurane and halothane in man 1976;55:709
  Interaction of epinephrine (correspondence) 1977;56:747
  see Hillyer KW
  White PF, Eger EI II. Dextroamphetamine and reserpine effects on halothane and cyclopropane anesthesia 1975;54:655
  White PF, Way WL et al. The effect of levodopa on halothane anesthetic requirement 1975;54:178
Johnstone RE. Anesthesiology continuing education review (book review) 1977;56:171
  Gutsche BB. Missionary anesthesia 1975;54:184
  Gutsche BB. Missionary anesthesia (correspondence) 1975;54:819
  Kulp RA, Smith TC. Effects of acute and chronic ethanol administration on isoflurane requirement in mice 1975;54:277
Jointer J, see Martz KV
Jones CJ, see Mirakhur RW
Jones CS. Advanced CPR: "death is one of two things" (letter) 1983;62:541
  Gas viscosity effects in anesthesia

Jones CS—*continued*
    1980;59:192
  Modification of a Bird Mark-14 ventilator for greater versatility (brief reports) 1976;55:879
  Vaporizers for ether (correspondence) 1978;57:147
Jones CW, see Calverley RK
  see Crawford AH
Jones DG. Recent perspectives on the organization of central synapses 1983;62:1100
Jones DJ, Hodgson BJ, Stehling LC, Zauder HL. Enflurane and uterine contractility in rabbits 1978;57:160
  see Lalka D
Jones EL, see Kaplan JA
Jones JF, Hendershot RJ. Compressed air-$O_2$-anesthetic mixture for the neonate 1977;56:127
  see Calkins JM
Jones JJ, Berry AJ. Effect of pancuronium on heart rate during isoflurane and nitrous oxide anesthesia (letter) 1984;63:166
Jones JR, see Rah KH
Jones LA, see Coetzee A
  see Philbin DM
Jones M, see Kim BY
Jones MD, see Donegan J
Jones MJW, see Booij LHDJ
Jones NL. Blood gases and acid-base physiology (book review) 1980;59:397
Jones PIE, Britt BA, Steward DJ, Volgyesi GA, Scott E. Tourniquet test as a predictor of malignant hyperthermia susceptibility (abstract) 1981;60:256
Jones RM, Detmer M, Hill AB, Bjoraker DG, Pandit U. Incidence of choledochoduodenal sphincter spasm during fentanyl-supplemented anesthesia 1981;60:638 (abstract) 1981;60:257
  Fiddian-Green R, Knight PR. Narcotic-induced choledochoduodenal sphincter spasm reversed by glucagon 1980;59:946
  Lumbar epidural anesthesia in patients with multiple sclerosis (letter) 1983;62:856
  Nahrwold ML, de Rosayro AM, Hill AB. Cardiovascular responses and changes in plasma cation levels associated with infusion of hyperosmolar urea solutions 1981;60:641
  Williams JP, Pearce AC. Pre- and postjunctional effects of neuromuscular blocking agents and their antagonists (letter) 1983;62:1137
Jones SEF, see Beasley JM
Jonson B, see Prakash O
Jordan R, see Westenskow DR
Jordan WS Ketamine and epilepsy (correspondence) 1976;55:447
  see Pace NL
  see Westenskow DR
Jørgensen BC, see Schmidt JF
Jørgensen [illegible], see Kromann B
Jorgenson NB, Hayden J. Sedation, local and general anesthesia in dentistry, third edition (book review) 1980;59:713
Jose AB, see Gallagher JD
Joseph MM, Shah K, Viljoen JF. Malignant hyperthermia associated with isoflurane anesthesia (letter) 1982;61:711
Joseph SI, see Shin B
Joshi C, Bruce DL. Thiopental and succinylcholine: action on intraocular pressure 1975;54:471
  see Linde HW
Joshi SM, Hehre FW. Peridural block complicating lumbar sympathetic block 1977;56:873
Jove F, Milliken RA
  Loss of anesthetic gases due to defective safety equipment (letter) 1983;62:369
Joyce JT, Roizen MF. Application of face mask does not increase plasma norepinephrine levels (abstract) 1981;60:257
Joyce TH III, see Keller F
Juang MS, Yonemura K, Morioka T, Tanaka I. Ketamine acts on the peripheral sympathetic nervous system of guinea pigs 1980;59:45
Juárez JB, see Gonzalez-Miranda F
Jurado RA, see Silvay G
Kacher EJ, see Fox F
Kachhawa S, see Shrivastava OP
Kacmarek RM, see Assmann DC
Kadis LB, see Katz J
Kafer ER, see Brown DR
Kahan BD, see Mathieu A
Kahn RC, Jascott D, Carlon GC, Schweizer O, Howland WS, Goldiner PL. Massive blood replacement: correlation of ionized calcium, citrate, and hydrogen ion concentration 1979;58:274
  see Carlon GC
  see Shoum S
Kahre J, see Chapin JW
Kaieda R, Maekawa T, Takeshita H, Maruyama Y, Shimizu H, Shimoji K. Effects of diazepam on evoked electrospinogram and evoked electromyogram in man 1981;60:197
Kakos GS, see Dasta JF
Kalbfleisch JH, see Asiddao CB
Kalia PK, Madan R, Saksenar, Batra RK, Gode GR. Epidural pentazocine for postoperative pain relief 1983;62:949
Källén B, see Ericson A
Kallichurum S, see Brock-Utne JG
Kallus FT, see Giesecke AH Jr
  see Samuelson RJ
  Wilcox JR, Jenkins MT. A plastic sleeve electrode (brief reports) 1975;54:698
Kalso EA, Lalla ML, Rosenberg PH, Tuominen MK, Santavirta S, Gripenberg J. Evaluation of the myotoxicity of bupivacaine in bier blocks—a biochemical and electron microscopic study 1983;62:796
Kamal MM, see DeBoer GE
Kamat RD. Use of Magill tube for passing nasogastric tube in anesthetized or comatose patients (brief reports) 1975;54:156
Kamath SA, see Ansari IA
Kamaya H, Hayes JJ Jr, Ueda I. Dissociation constants of local anesthetics and their temperature dependence
  see Ueda I
Kaminsky L, see Harrison GG
Kampine JP, see Bosnjak ZJ
  see Kotrly KJ
  see Palmer SK
  see Turner LA
Kampmann J, see Bochner F
Kanakoudes PS, see Balamoutsos NG
Kane EW, see Goldzimer EL
Kane MA, see Berry AJ
Kane PB, see Arandia HY
  see Grogono AW
  see King DO
  see Nerothin DD
Kane RE. Neurologic deficits following epidural or spinal anesthesia 1981;60:150
Kanel JS, see Calkins JM
  see Eskelson CD
  see Hameroff SR
Kang SB. Continuous thoracic epidural anesthesia for biliary tract surgery and postoperative pain relief in a patient with cystic fibrosis 1982;61:793
Kang YG, Abouleish E, Caritis S. Prophylactic intravenous ephedrine infusion during spinal anesthesia for cesarean section 1982;61:839
Kaniaris P, Batrinos M, Varonos D, Fassoulaki A. Cholinergic action of thiopental on the hypothalamo-hypophyseal axis 1981;60:310
  Fassoulaki A, Liarmakopoulou K, Dermitzakis E. Serum cholinesterase levels in patients with cancer 1979;58:82
  Katsilambros N, Castanas E et al.

  Relation between glucose tolerance and serum insulin levels in man before and after thiopental intravenous administration 1975;54:718
Kano T, Cowan GSM, Smith RH. Electroanesthesia (EA) studies: EA produced by stimulation of sensory nerves of the scalp in Rhesus monkeys 1976;55:536
  see Smith RH
Kant YG, see Martin DJ
Kaplan J, see Brooks JL Jr
Kaplan JA. Cardiac anesthesia (book review) 1979;58:354
  Dunbar RW, Bland JW et al. Propranolol and cardiac surgery: a problem for the anesthesiologist? 1975;54:571
  Dunbar RW, Hatcher CR. Diagnostic value of the $V_5$ precordial electrographic lead: a case report 1978;57:364
  Dunbar RW. Propranolol and surgical anesthesia 1976;55:01
  Guffin AV, Jones EL, Kates RA, Holbrook GW. Verapamil and myocardial preservation in patients undergoing coronary artery bypass surgery (abstract) 1984;63:230
  Miller ED, Bailey DR. A comparative study of enflurane and halothane using systolic time intervals 1976;55:263
  Miller ED, Gallagher EG. Postoperative analgesia for thoracotomy patients 1975;54:773
  see Barbieri LT
  see Cohen JA
  see Guffin AV
  see Kates RA
  see Lieberman RW
  see Lonergan JG
  see Waller JL
  see Welti RS
  Vasodilator treatment of heart failure after cardiopulmonary bypass (case history) (guest discussion) 1975;54:842
  Wells PH. Early diagnosis of myocardial ischemia using the pulmonary arterial catheter 1981;60:789
Kaplan R, Duncalf D, Cizmar S. *Aspergillus* pancarditis and cardiac arrest during anesthesia 1981;60:440
  see Shapiro LA
Kaplan RF, Cuddeback J, Orsine L, Purkey I. Transfusions for jehovah's witnesses (letter) 1983;62:122
  Paulus DA. Error in sampling of exhaled gases (letter) 1983;62:955
  see Martyn JAJ
  see Pyles ST
Kapur PA, Flacke WE. Epinephrine arrhythmogenic dose during halothane anesthesia and plasma levels of verapamil (abstract) 1981;60:258
  Flacke WE, Olewine SK. Comparison of effects of isoflurane versus enflurane on cardiovascular and catecholamine responses to verapamil in dogs (abstract) 1982;61:193
  Norel EJ, Cohen GR, Dajee H. Verapamil administration after high dose fentanyl with or without chronic nifedipine therapy in man (abstract) 1984;63:231
  Norel EJ, Dajee H, Cimochowski G. Verapamil treatment of intractable ventricular arrhythmias after cardiopulmonary bypass 1984;63:460
Karam AM, see Baraka A
Karasic LH, see Walajahi FW
Karenbelkar DJ, see Azar I
Kareti RKP, Kim YD, Chen J, Wallace R. Macnamara TE. An analysis of perioperative factors influencing early extubation following coronary artery bypass graft (CABG) surgery (abstract) 1984;63:232
Karis JH. Hypotension caused by failure of an infusion pump 1979;58:250
  Menzel DB. Inadvertent change of volatile anesthetics in anesthesia machines 1982;61:53
  O'Neal F, Weitzner SW. Alteration of halothane in heated humidifiers (letter) 1980;59:518
  see Bloch EC
  see Karis JP
Karis JP, Burton LW, Karis JH. A quantitative neuromuscular blockade monitor 1980;59:308
Karlström G, see Modig J
Karp RB, see Reves JG
Kartha RK, see Mathru M
Kassell N, see Sokal MD
Kata J, see Greensite FS
Katele G, see Lichtenthal PR
Katele GV, see Meyer RM
Kates RA, Kaplan JA. Cardiovascular responses to verapamil during coronary artery bypass graft surgery 1983;62:821
  Kaplan JA, Hug CC, Guyton R, Dorsey LM. Hemodynamic interactions of verapamil and isoflurane in dogs (abstract) 1982;61:194
  see Kaplan JA
  see Saltzman LS
  Zaidan JR, Kaplan JA. Esophageal lead for intraoperative electrocardiographic monitoring 1982;61:781
Katsilambros N, see Kaniaris P
Kattine AA, see Ozdil T
Katz H, Machida RC, Wootton DG et al. A technic of general anesthesia for blepharoplasty and rhytidectomy 1976;55:165
Katz J, Benumof J, Kadis LB. Anesthesia and uncommon diseases: pathophysiology and clinical correlations, second edition (book review) 1981;60:T20
  see Quimby KL
Katz JD, see Akutagawa T
  see Barash PG
Katz RL. Interaction of epinephrine (correspondence) 1977;56:747
  see Chalon J
  see Conner JT
  see Eisenberg M
  see Graham CW
  see Lee C
  see Raj PP
  see Sohn YZ
  see Stirt JA
  see Zeh DW
  Stirt J, Murray AL, Lee C. Neuromuscular effects of atracurium in man 1982;61:730
Katzenelson R, see Perel A
Kaufer H, see Waldman J
Kaufman JJ, see Benson DW
Kaufman L, Sumner E. Medical problems and the anaesthetist—current topics in anaesthesia, Volume 4 (book review) 1981;60:69
Kaufman RD, see Gabathuler ML
  see Stirt JA
Kauste A, see Korttila K
Kawabori I, see Morray JP
Kawahara M, Kitahata LM, Collins JG, Homma E. Thiopental suppression of neurons of the nucleus reticularis gigantocellularis of the cat 1982;61:763
  see Kikuchi H
Kawamura R, see Bidwai AV
  see Hill GE
  Stanley TH, English JB, Hill GE, Liu WS, Webster LR. Cardiovascular responses to nitrous oxide exposure for two hours in man 1980;59:93
  Wong KC, Hodges MR. Intravenous potassium chloride in hypokalemic dogs pretreated with digoxin 1978;57:108
Kawar P, see Dundee JW
Kay J, Kay MC. Alcuronium for open-eye injuries (letter) 1984;63:543
  Rouman WC. Technique for rejoining cut epidural catheter (letter) 1984;63:783
Kay JC, see Byrick RJ
Kay MC, see Kay JC
Kayerker UM, Dick MM. Phrenic nerve

Kayerher UM—*continued*
  paralysis following interscalene brachial plexus block 1983;62:536
Keaney AE, see Fyman PN
Keats AS, see Koska AJ III
  see Slogoff S
Keegan CR, see Philbin DM
  see Rosow CE
Keenan RL, see Shiroka A
Kehlet H, see Hasselstrøm LJ
Keller F, Joyce TH III. Uterine rupture with the use of vaginal prostaglandin $E_2$ suppositories (letter) 1983;62:1046
Kelley M, see Baden JM
Kellner G, see Lanz E
Kelly PJ, see Galindo A
Kemi C, see Yanagida H
Kemp J, see Ward CF
Kenefick JP, Wexler HR, Gelb AW. Intravenous Labetalol in the management of postoperative hypertension (abstract) 1982;61:195
Kennedy J, see Diamant M
Kennedy PJ, Feingold A, Wiener EL et al. Analysis of tasks and human factors in anesthesia for coronary artery bypass 1976;55:374
Kennedy RL. Management of epidural analgesia in childbirth (book review) 1984;63:705
  Vocal cord paresis following endotracheal intubation (questions and answers) 1977;56:321
Kennedy SF, see Hanowell ST
Kent B, see Kent DW
Kent DW, Halsey MJ, Eger EI II, Kent B. Isoflurane anesthesia and pressure antagonism in mice 1977;56:97
Kent G, see Kolton M
Kerem DH, see Bitterman H
Kerrick GL, see Su JY
Keszler H, see Klain M
Ketcham TR, see Bjoraker DG
Keyman HJ, see Ivankovich AD
Keys TE. Dr. Arthur Ernest Guedel 1975;54:442
  Dr August Karl Gustav Bier 1975;54:322
  Dr. Carl Koller 1975;54:247
  Harvey Cushing, Historical vignettes (correspondence) 1975;54:518
  Howard Wilcox Haggard 1975;54:654
  Rudolph Matas 1975;54:29
  Yandell Henderson 1975;54:806
Khalil SN, Williams JP, Bourke DL. Management of a malignant hyperthermia susceptible patient in labor with 2-chloroprocaine epidural anesthesia 1983;62:119
Khambatta HJ, see Stone JG
  Stone JG, Khan E. Propranolol alters renin release during nitroprusside-induced hypotension and prevents hypertension on discontinuation of nitroprusside 1981;60:569
  Stone JG, Matteo RS, Khan E. Propranolol premedication blunts stress response to nitroprusside hypertension 1984;63:125
Khan E, see Khambatta HJ
Khan RM, see Khan TZ
Khan TZ, Khan RM. Changes in serum potassium following succinylcholine in patients with infections 1983;62:327
Kharkevich DA. Pharmacology of ganglionic transmission, Volume 53 (book review) 1980;59:957
Khine HH, Naidu R, Cowell H, MacEwen GD. A method of blood conservation in jehovah's witnesses: incirculation diversion and refusion 1978;57:279
Khoo SS, see Abboud TK
Kiefer L, see Paegle RD
Kieraszewicz HT, see Knill RL
Kikuchi H, Kitahata LM, Collins JG, Kawahara M, Nio K. Halothane-induced changes in neuronal activity of cells of the nucleus reticularis 1980;59:897
Kileff ME, James FM III, Dewan MD, Floyd HM. Neonatal neurobehavioral responses after epidural anesthesia for cesarean section using lidocaine and bupivacaine 1984;63:413
Kilpatrick A. Practical dental anaesthesia (book review) 1980;59:714
Kilpatrick ME, Girgis NI. Meningitis—a complication of spinal anesthesia 1983;62:513
Kim BY, Michalik R, Jones M, Hanowell S, Macnamara TE. Protamine effect on hypoxic pulmonary vasoconstriction in dogs (abstract) 1981;60:259
  see Frost EAM
Kim C, see Albert CA
Kim DI, see Sprague DH
Kim JM, Arakawa K, Bliss J. Arterial cannulation: factors in the development of occlusion 1975;54:836
  Arakawa K, VonLintel T. Use of the pulse-wave monitor as a measurement of diagnostic sympathetic block and of surgical sympathectomy 1975;54:289
  Buakham C, McAmis F. Supine hypotensive syndrome caused by intra-abdominal mass: a case report (brief reports) 1976;55:887
  Goto H, Arakawa K. Duration of bupivacaine intradermal anesthesia when the bupivacaine is mixed with chloroprocaine 1979;58:364
  Hackman L. Anesthesia for untreated hyperthyroidism: report of three cases 1977;56:299
  LaSalle AD, Parmley RT. Sympathetic recovery following lumbar epidural and spinal analgesia 1977;56:352
  Robinson J. Uneven epidural analgesia—early diagnosis and correction: case reports 1975;54:593
  see Buakham C
  see Littell L
  The tracheal tube cuff pressure stabilizer and its clinical evaluation 1980;59:291
Kim JW, Smith PH. Timolol-induced bradycardia 1980;59:301
Kim KC, see Abboud TK
Kim SI, see Park WY
Kim SS, Hodgkinson R. Acute ethanol intoxication and its prolonged effect on a full-term neonate (brief reports) 1976;55:602
Kim YD, Nematzadeh D, Kot PA, Lees DE, Rose JC, Macnamara TE. Effects of halothane on systolic endocardial intramyocardial pressure (ENDO-IMP) measured simultaneously from ischemic and normoxic segments of canine myocardium (abstract) 1984;63:233
  see Elsten JL
  see Kareti RKP
  see Lee JK
Kimelberg HK, see Popp AJ
Kimovec MA, see Berry AJ
Kimura T, see Fujita T
  see Yamamura T
King BD, see Sklar GS
King DO, Kane PB. Blood clot formation during multiple cardiopulmonary bypass procedures necessitated by massive hemorrhage 1978;57:273
King H, see Moorthy SS
King J. Prolonged apnea after succinylcholine in a dental outpatient (case history) (guest discussion) 1976;55:738
King LS. Why not say it clearly (book review) 1979;58:262
King RD, see Hilgenberg JC
King SB III, see Waller JL
  Vasodilator treatment of heart failure after cardiopulmonary bypass (case history) (guest discussion) 1975;54:842
King WH, Gloyna DF, Patten EV, Huber PA. Dilution of packed red blood cells: saline or Ringer's lactate (abstract) 1984;63:234
Kingston HGG, Harrison MW, Smith JD. Laryngotracheoesophageal cleft—a problem of airway management 1983;62:1041
  Hirshman CA. Perioperative management of the patient with asthma 1984;63:844
Kinley CE, see Moffitt EA
Kinney JM, see Richards JR

see Rosenbaum SH
Kinoshita O, Aoki A, Yamamura T, Yamashita S. Plasma glucagon levels during spinal anesthesia and surgery in a glucagon-deficient patient 1983;62:846
Kirby R, Graybar GB. International anesthesiology clinics, intermittent mandatory ventilation, Volume 18, Summer 1980 (book review) 1980;59:957
Kirby RR, see Gooding JM
Kirimli BI, see Ng TY
Kirsh M, see Bjoraker DG
see Knight PR
Kiruluta G, see Baxter AD
Kissin I, Jebeles JA. Pentobarbital antagonizes the effect of morphine on cardiac acceleration response to noxious stimulation 1984;63:669
Motomura S, Aultman DF, Reves JG. Inotropic and anesthetic potencies of etomidate and thiopental in dogs 1983;62:961
see Motomura S
see Reves JG
see Tosone SR
Kistner JR, Longnecker DE, Miller ED Jr, Lescanic AD. Limitations of the cyanide electrode for use in plasma and whole blood 1979;58:457
see Delaney TJ
Kitahata LM, Collins JG. Narcotic analgesics in anesthesiology (book review) 1982;61:480
see Akutagawa T
see Barash PG
see Collins JG
see Homma E
see Kawahara M
see Kikuchi H
see Suzukawa
Kitani Y, see Fujita T
Kittle CF, see El-Baz N
Kitz RJ, see Attia RR
Kitzmiller JL, see Datta S
Kivalo I, see Lehtinen AM
Kiykhak MM, see Rosenberg H
Klain M, Keszler H, Nordin U. Is jet ventilation without cuffed tube safe? (abstract) 1982;61:195
see Benjaminsson E
see Schuster DP
Klein E, see Perel A
Klein EF. Complete obstruction of an armored endotracheal tube (correspondence) 1975;54:350
Klein F, see Smith NT
Klein J, see Koren G
Klein SL, Camenzind T. Hazards of bottle adaptors for vaporizers (correspondence) 1978;57:596
Klemic N, see Mackenzie CF
Klemm JE, see Ravindran RS
Klick JM, see Posner MA
Klide AM, Kung SH. Veterinary acupuncture (book review) 1978;57:291
Klimov I, see Heyman HJ
Kline J. Biological foundations of biomedical engineering (book review) 1979;58:161
Klineberg PL, see Martin DE
Klowden AJ, see Ivankovich AD
Klowden RJ, see Braverman B
Knape H, see Zegveld C
Knapp R, Cohen PJ. "Bedbug infestation" as a complication of epidural anesthesia (letter) 1979;58:531
Knapp RB, see Smith DJ
Knapp RM, see Mallampati SR
Knight PR, Kroll DA, Nahrwold ML, Denlinger JK, Kirsh M, Welter LO, Hill AG, Cohen PJ, Ronfeld RA. Comparison of cardiovascular responses to anesthesia 1980;59:130
see Bjoraker DG
see Jones RM
Knill RL, Clement JL, Kieraszewicz HT, Dodgson BG. Assessment of two noninvasive monitors of arterial oxygenation in anesthetized man 1982;61:582
Prins L, Strupat J, Clement J. Nitrous oxide and vaporizer outputs, transient or continuous effect? (letter) 1980;59:808
see Lam A
see Prato FS
Knopp TJ, see Beynen FM
Koblin DD, Deady JE, Nelson NT, Eger EI II, Bainton CR. Mice tolerant to nitrous oxide are not tolerant to barbiturates 1981;60:138
Eger EI II. Cross-mating of mice selectively bred for resistance or susceptibility to nitrous oxide anesthesia: potencies of nitrous oxide in offspring 1981;60:646
Eger EI II, Johnson BH, Collins P, Terrell RC, Speers L. Are convulsant gases also anesthetics? 1981;60:464
Lurz FW, O'Connor B, Nelson NT, Eger EI II, Bainton CR. Potencies of barbiturates in mice selectively bred for resistance or susceptibility to nitrous oxide anesthesia 1984;63:35
see Deady JE
see Eger EI II
see Gillman MA
see Harper MH
Waskell L, Watson JE, Stokstad ELR, Eger EI II. Nitrous oxide inactivates methionine synthetase in human liver 1982;61:75
Kodali SV, see Henling CE
Koehler RC, see Donegan J
Koga Y, see Iwatsuki N
Kohli V, see Ansari IA
Kohlmoos HW, see Baron SH
Koht A. A potential hazard of thermodilution injection (letter) 1982;61:544
Mulvehill J, Patt M. Hemodynamic effects of high dose thiopental for induction of anesthesia (abstract) 1981:60:260
Kok K, see Bovill JG
Koka BV, Jeon IS, Andre JM, MacKay I, Smith RM. Postintubation croup in children 1977;56:501
Koller ME, Smith RB, Sjöstrand U, Breivik H. Effects of hypo-, normo-, and hypercarbia in dogs with acute cardiac tamponade 1983;62:181
Kolling JB, see van der Starre PJA
Kolobow T, see Gattinoni L
Kolton M, Cattran CB, Kent G. Volgyesi G, Froese AB, Bryan AC. Oxygenation during high-frequency ventilation compared with conventional mechanical ventilation in two models of lung injury 1982;61:323
Komai H, Rusy BF. Differences in the myocardial depressant action of thiopental and halothane 1984;63:313
Rusy BF. Effect of halothane on rested-state and potentiated-state contractions in rabbit papillary muscle: relationship to negative inotropic action 1982;61:403
Komatsu T, see Kubal K
Shibutani K, Bizzarri DV. Critical level of oxygen delivery in anesthetized man (abstract) 1982;61:196
Konchigeri HN. Hemodynamic effects of heparin in patients undergoing cardiac surgery (abstract) 1984;63:235
Levitsky S. Anesthetic considerations for pericardectomy in uremic pericardial effusion 1976;55:378
Tay CH. Influence of pancuronium on potassium efflux produced by succinylcholine 1976;55:474
Kondo K, O'Reily LP, Choita J Jr. Air embolism associated with an introducer for pulmonary arterial catheters 1984;63:871
Konichezky S, see Soroker D
Kono K, Philbin DM, Coggins CH, Moss J, Rosow CE, Schneider RC, Slater EE. Renal function and stress response during halothane or fentanyl anesthesia 1981;60:552
(abstract) 1981;60:260
Koopman D, see Natua J
Koot HWJ, see Gencarelli PJ
Kopman AF. Effect of $PaCO_2$ on $O_2$ consumption during cardiopulmonary bypass (correspondence) 1976;55:888

Kopman AF—*continued*
  Epstein RH, Flashburg MH. Use of 100-hertz tetanus as an index of recovery from pancuronium-induced non-depolarizing neuromuscular blockade 1982;61:439
  How do benefits of hemodilution balance $O_2$ reduction? (correspondence) 1976;55:887
  Wollman SB, Ross K et al. Awake endotracheal intubation: a review of 267 cases 1975;54:323
Kopman EA. A simple method for verifying endotracheal tube placement 1977;56:123
  Ferguson TB. Intraoperative monitoring of femoral artery pressure during replacement of aneurysm of descending thoracic aorta 1977;56:603
  Ferguson TB. Pulmonary edema following cardiopulmonary bypass 1978;57:367
  Hemoptysis associated with the use of a flow-directed catheter 1979;58:153
  Ramirez-Inawat RC. Intra-aortic balloon counterpulsation for right heart failure 1980;59:74
  Ramirez-Inawat RC. Persistent electromechanical cardiac arrest following administration of cardioplegic and glucose-insulin-potassium solutions 1980;59:69
  Relief of pulmonary congestion by sublingual nitrogylcerin in patients with mitral valve disease 1979;58:143
  Scavenging of potassium cardioplegic solution to prevent hyperkalemia in hemodialysis-dependent patients 1983;62:780
Kopriva CJ. Anesthesia for thoracic surgery (book review) 1983;62:372
  see Barash PG
  see Suzukawa M
Koren G, Crean P, Goresky G, Klein J, Villamater J, MacLeod SM. Irreversible binding of fentanyl (F) to the cardiopulmonary bypass (CPBP) (abstract) 1984;63:236
  Goresky G, Crean P, Klein J, MacLeod SM. Pediatric fentanyl dosing based on pharmacokinetics during cardiac surgery 1984;63:577
Korevaar WCl, Burney RG, Moore PA. Convulsions during stellate ganglion block: a case report 1979;58:329
Korthuis RJ, see Sawyer DC
Korttila K, Kauste A, Auvinen J. Comparison of domperidone, droperidol, and metoclopramide in the prevention and treatment of nausea and vomiting after balanced general anesthesia 1979;58:396
Kory WP, see Gravenstein JS
Kosanin R. Transtracheal or translaryngeal? (letter) 1983;62:371
Kosek JC, see Cook TL
Koska AJ III, Kramer WG, Romagnoli A, Keats AS, Sabawala PB. Pharmacokinetics of high-dose meperidine in surgical patients 1981;60:08
Koski DW, Fraser JG. Pruritis following spinal anesthesia 1980;59:157
Koski WS, see Benson DW
Kot PA, see Kim YD
Kothary SP, see Domino EF
  see Pandit SK
  see Pandit UA
  see Zsigmond EK
Kotrly KJ, Ebert TJ, Vucins EJ, Roerig DL, Kampine JP. Baroreceptor reflex control of heart rate during morphine sulfate/diazepam/$N_2O$-$O_2$ and fentanyl/diazepam/$N_2O$ $O_2$ anesthesia in man (abstract) 1984;63:237
  Kotter GS, Mortara D, Kampine JP. Intraoperative detection of myocardial ischemia with an ST segment trend monitoring system 1984;63:343
  see Kotter GS
Kotter GS, Bernstein JS, Kotrly KJ. ECG changes detect coronary artery bypass graft occlusion without hemodynamic instability 1984;63:1133
  see Kotrly KJ
Kouchoukos NT, see Lell WA
  see Samuelson PN
Kozody R, Cumming M, Palahniuk RJ. Spinal cord blood flow following subarachnoid block with and without epinephrine (abstract) 1984;63:238
Krall JM, see Myerberg DZ
Kraman SS, see Huang KC
Kramer WG, see Koska AJ III
Krantz EM, Viljoen JF, Schermer R, Cañas MS. Mitral valve prolapse 1980;59:379
Kraus JW, see Manchikanti L
Krause PD. Statistical analysis of pH data (correspondence) 1978;57:143
Kraynack BJ, Lawson NW, Gintautas J, Tjay HT. Effects of verapamil on indirect muscle twitch responses 1983;62:827
  see Lawson NW
Krechel SLW, Ramirez-Inawat RC, Fabian LW. Anesthetic considerations in pseudoxanthoma elasticum 1981;60:344
Kremer PE, see Cahalan MK
Krenzelok EP, Parker WA. Dextran 40 anaphylaxis (editor's choice) 1975;54:736
Kretzschmar R, see Lehmann HD
Kreul JF, see Taylor CA
Kripke BJ, Finck AJ, Shah NK et al. Naloxone antagonism after narcotic-supplemented anesthesia 1976;55:800
  see Shah NK
  see Snow JC
  Sherwin RP. Nitrogen dioxide exposure—influence on rat testes 1984;63:526
Krishna G. Neurofibromatosis, renal hypertension, and cardiac dysrhythmias (case history) 1975;54:542
  Paradise RR. Mechanisms of chronotropic effects of volatile inhalation anesthetics 1977;56:173
  see Dierdorf SF
  see Haselby KA
  see Rao CC
  see Roesch C
  see Vulliemoz Y
Kroesen GA, Haid BC. Fatal complications from swallowed denture following prolonged endotracheal intubation: a case report (brief report) 1976;55:438
Kroll DA, see Knight PR
Kromann B, Jørgensen J, Larsen S. Diazepam in an oil emulsion (letter) 1982;61:544
Kruger R, see van der Vusse GJ
Kruk ZL, Pycock CJ. Neurotransmitters and drugs (book review) 1980;59:521
Krupin T, see Cross DA
Krusske JA, see Bassell GM
Kryc J, see Reitz J
Kubal K, Komatsu T, Sanchala V, Kumar V, Shibutani K. Trendelenburg position used during venous cannulation increases myocardial oxygen demand (abstract) 1984;63:239
Kuck EJ, see James CF
Kuhn J, see Lee DS
Kuhnert BR, Harrison MJ, Linn PL, Kuhnert PM. Effects of maternal epidural anesthesia on neonatal behavior 1984;63:301
  Kuhnert PM, Reese ALP, Philipson EH, Rosen MG. Maternal and neonatal elimination of CABA after epidural anesthesia with 2-chloroprocaine during parturition 1983;62:1089
  see Abboud TK
Kuhnert L, see Berman ML
Kuhnert PM, see Kuhnert BR
Kulczycki L, see Harnik E
Kulp RA, see Johnstone RE

Kumar N, Pandit SK, Detmer MD. Pulmonary lesions after antacid and cimetidine aspiration (abstract) 1980;59:447
Kumar SM, Pandit SK, Jackson PF. Recall following ketamine anesthesia for open-heart surgery: report of a case 1978;57:267
Kumar V, see Kubal K
Kundsin RB, see Spaepen MS
Kung SH, see Klide AM
Kunjappan V, see Brown EM
Kuramoto T, Sakabe T. Comparison of success of jugular versus basilic vein technics for central venous pressure catheter positioning (brief reports) 1975;54:696
Kuribayashi H, see Shimoji K
Kurlan RM, see Dobkin AB
Kushins LG, see Munson ES
  see Wollman SB
Kutner MH, see Ingram C
  see Paulsen AW
  see Sung YF
Kuypers RSM, see van Poorten JF
Kwan AM, Albert SN. Hypothermia during cystoscopy (correspondence) 1977;56:326
Kwik RSH, see Francis RN
Kwon P, Schachter EN, Warshaw J. Mobile respiratory assistor: evaluation of a new ventilator for neonatal transport 1978;57:729
LaBlonde P, see Ravindran R
Laflin MJ, Tobey RE, Reves JG. Anesthetic considerations in patients with gas gangrene 1976;55:247
LaForce FM, see Manawadu BR
Lagerkranser M, see Rudehill A
Lahiri S, see Fitzgerald RS
Lake CL. Anesthesia and pericardial disease 1983;62:431
  Anesthesia and Wegener's granulomatosis: case report and review of the literature 1978;57:353
  Anesthesia in patients with ischaemic heart disease (book review) 1983;62:1053
  Cardiac tamponade and transmural myocardial pressures (letter) 1984;63:94
  Curare sensitivity in steroid-treated myasthenia gravis: a case report 1978;57:132
  see Delaney TJ
  see Hecker BR
  Sellers TD, Nolan SP, Crosby IK, Wellons HA Jr, Crampton RS. Energy dose and other variables possibly affecting ventricular defibrillation during cardiac surgery 1984;63:743
Lake CR, see Chernow B
Laks H, see Barash PG
Lalka D, see McNamara PJ
  Vicuna N, Burrow SR, Jones DJ, Luden TM, Haegele KD, McNay JL. Bupivacaine and other amide local anesthetics inhibit the hydrolysis of chloroprocaine by human serum 1978;57:534
Lalla ML, see Kalso EA
Lalli AF, see Gottlieb A
Lam A, Knill RL. Effects of nitrous oxide on the ventilatory response to enflurane (abstract) 1981;60:261
Lam AM, Gelb AW. Cardiovascular effects and gas exchange during isoflurane-induced hypotension for cerebral aneurysm surgery (abstract) 1982;61:197
  Gelb AW. Cardiovascular effects of isoflurane-induced hypotension for cerebral aneurysm surgery 1983;62:742
  Gelb AW. Succinylcholine and intracranial pressure—a cause for "pause" (letter) 1984;63:620
  Manninen PH. Is morphine-$N_2O$ technique suitable for the seated position? (letter) 1984;63:169
  Nicholas JF, Manninen PH. Influence of succinylcholine on lumbar cerebral spinal pressure in man (abstract) 1984;63:240
  see Gelb AW
  see Manninen PH
Lamb JD. Aspiration or carbon dioxide embolism? (letter) 1983;62:368
Lambert DH. Cephalosporin hepatitis (letter) 1980;59:806
  Deane RS, Mazuzan JE Jr. Anesthesia and the control of blood pressure in patients with spinal cord injury 1982;61:344
  see Abajian JC
  see Datta S
Lampe KM, Gelb AW, Wexler HR, Stein J, Spoerel WE. Assessment of inversed ratio ventilation in the adult respiratory distress syndrome (abstract) 1984;63:241
Lampert BA, Gould DB. Effect of nitrous oxide on vaporizer aberrance (letter) 1983;62:956
  see Gould DB
Land PC, see Baden JM
Land SJ, see Maze M
Landmark SJ, Muldoon SM, Nolan NG et al. Sequential blood volume changes in patients undergoing total hip arthroplasty 1975;54:391
Landry LD, Emerson CW, Philbin DM, Palacios I, Goldblatt A, Block P. The effect of nitrous oxide on pulmonary vascular resistance in children (abstract) 1980;59:548
Landymore R, see Moffitt EA
Lane GA, Steude GM, Pashley NRT. Anesthesia for a patient with a tracheal T-tube stent 1981;60:218
Lane PE, see Sivarajan M
Lang DW, Pilon RN. Naloxone reversal of morphine-induced biliary colic 1980;59:619
Langford K, see Corssen G
Lanz E, Ruiz B, Schlereth H. Local anesthetics and pulmonary venous admixture in pregnant and nonpregnant sheep 1979;58:318
  Simko G, Theiss D, Glocke MH. Epidural buprenorphine—a double-blind study of postoperative analgesia and side effects 1984;63:593
  Theiss D, Jankovic D. The extent of blockade following various techniques of brachial plexus block 1983;62:55
  Theiss D, Kellner G, Zimmer M, Staudte HW. Assessment of motor blockade during epidural anesthesia 1983;62:889
  Theiss D, Riess W, Sommer U. Epidural morphine for postoperative analgesia: a double-blind study 1982;61:236
Laravuso RB, see Atlee JL III
Larsen S, see Kromann B
Larson GF, Hurlbert BJ, Wingard DW. Physostigmine reversal of diazepam-induced depressions 1977;56:348
Lasagna L, see Weis OF
LaSalle AD, see Kim JM
Lassale B, see Ang ET
Latasch L, Probst S, Dudziak R. Reversal by nalbuphine of respiratory depression caused by fentanyl 1984;63:814
Lathrop GD, see Stanley TH
Latta W, see Morita S
Latto IP, see Rosen M
Laughlin RP, McMichan JC. Adjustment of PEEP according to continuous measurement of mixed venous $O_2$ saturation ($S_{\bar{v}}O_2$) (abstract) 1984;63:242
Laver MB. Management of patient with hypokalemia on diuretic therapy (questions and answers) 1976;55:276
  What route of administration for $K^+$ solutions? (correspondence) 1976;55:895
Lavies NG. Coagulability after hip surgery (letter) 1984;63:1143
Lavin MJ, see Ido Y
Lavine LM, see Braverman B
Lawin P, see Van Aken H
Lawrence AM, see Hassan SZ
Lawrence J, see Bourke DL

Laws ER Jr, see Messick JM Jr
Laws HL, see Gelman S
Lawson NW, Kraynack BJ, Gintautas J. Neuromuscular transmission and verapamil (letter) 1983;62:1048
  Rogers D, Seifen A, White A, Thompson DS. Intravenous procaine as a supplement to general anesthesia for carbon dioxide laser resection of laryngeal papillomas in children 1979;58:492
  see Flacke JW
  see Kraynack BJ
  Thompson DS, Nelson CL et al. A dosage nomogram for sodium nitroprusside-induced hypotension under anesthesia 1976;55:574
  Thompson DS, Nelson CL et al. Sodium nitroprusside-induced hypotension for supine total hip replacement 1976;55:654
Lazerson J, see Stengert KB
Leaman DM, see Shenoy PN
Leanza R. Problems with anesthetic and respiratory therapy equipment (book review) 1984;63:172
Lear E, Jadwat C, Bough L et al. Atypical pseudocholinesterase: a clinical report 1976;55:243
  see Azar I
  see Casthely PA
  see Seravalli EP
Lear S, see Casthely PA
Lebowitz PW, Cote ME, Daniels AL, Martyn JAJ, Teplick RS. Comparative cardiovascular effects of midazolam and thiopental in healthy patients (abstract) 1982;61:198
  Cote ME, Daniels AL, Ramsey FM, Martyn JAJ, Teplick RS, Davison JK. Comparative cardiovascular effects of midazolam and thiopental in healthy patients 1982;61:771
  Ramsey FM, Savarese JJ, Ali HH, deBros FM. Combination of pancuronium and metocurine: neuromuscular and hemodynamic advantages over pancuronium alone 1981;60:12
  Ramsey FM, Savarese JJ, Ali HH. Potentiation of neuromuscular blockade in man produced by combinations of pancuronium and metocurine or pancuronium and *d*-tubocurarine 1980;59:604
  see Ali HH
  see Martyn JAJ
  see Ramsey FM
Lebrun M, see Delisle S
Lechtman A, see Carden E
Lecky JH. The mechanical aspects of anesthetic pollution control 1977;56:769
Ledingham IM, MacKay C. Jamieson & MacKay's Textbook of surgical physiology, third edition (book review) 1980;59:83
Ledingham IMcA. Recent advances in intensive therapy (book review) 1979;58:66
Lee ASJ, see Lee C
Lee C, Barnes A, Nagel EL. Neuroleptanalgesia for awake pronation of surgical patients 1977;56:276
  Chen D, Nagel EL. Neuromuscular block by antibiotics: polymyxin B 1977;56:373
  Katz RL. Fade of neurally evoked compound electromyogram during neuromuscular block by *d*-tubocurarine 1977;56:271
  Katz RL, Lee ASJ. A new instrument for continuous recording of the evoked compound electromyogram in the clinical setting 1977;56:260
  see Katz RL
  see Lippmann M
  see Steinbrook RA
  see Stirt JA
  see Yang E
  Succinylcholine neuromuscular block reexamined (letter) 1980;59:633
  Train-of-four-fade and edrophonium antagonism of neuromuscular block by succinylcholine in man 1976;55:663
  Yang E, Katz RL. Clinical neuromuscular pharmacology of BW 33A (abstract) 1982;61:199
  Yang E, Katz RL. Predetermination of dose requirement of pancuronium 1980;59:722
  Yang E. Predetermination of dose requirement of pancuronium and quantitative assessment of minimal and maximal neuromuscular block in the clinical setting (abstract) 1980;59:549
Lee CM. Acute hypotension during laparoscopy (case report) 1975;54:142
  Gildea JE Laryngotracheal residue during endotracheal anesthesia 1976;55:392
  Grossman LB. Laceration of left pulmonary artery during mediastinoscopy 1977;56:226
  Train-of-4 quantitation of competitive neuromuscular block 1975;54:649
  Unusual reaction to methyl methacrylate monomer (letter) 1984;63:372
  Yeakel AE. Patient refusal of surgery following Innovar premedication 1975;54:224
Lee DC, see Coran AG
Lee DS, Kuhn J, Shaffer MJ, Weintraub HD. Migration of tips of central venous catheters in seated patients 1984;63:949
  Lichtmann MW, Weintraub HD. Effect of PEEP on air embolism during sitting neurosurgical procedures (abstract) 1981;60:262
Lee HC, Andree RA. Cervical spondylosis and difficult intubation 1979;58:434
Lee HS, see Smith DJ
Lee JA, Atkinson RS. Sir Robert MacIntosh's lumbar puncture and spinal analgesia (intradural and extradural) (book review) 1979;58:355
Lee JH, Salvatore A. Innominate artery compression stimulating cardiac arrest during mediastinoscopy: a case report 1976;55:748
Lee JJ, see Howie MB
Lee JK, Hanowell S, Kim YD, Macnamara TE. Morphine-induced respiratory depression following bilateral carotid endarterectomy 1981;60:64
Lee K, Abrahamson S, Naik N. Jet ventilation of one lung for laser resection of bronchial tumor 1984;63:957
Lee KS, Park SS. Effect of halothane, enflurane, and nitrous oxide on tracheal ciliary activity in vitro 1980;59:426
Lee KW, see Schwartz AJ
Lee PKY, Modell JH, Andersen TW et al. Incidence of prolonged pain relief following acupuncture 1976;55:229
  see Modell JH
Lee R, see Munson ES
Lee TS, Wright BD. Flexible fiberoptic bronchoscope for difficult nasogastric intubation 1981;60:904
Lee VS, Burns RS, Dubois M, Cohen MR. Clearance from cerebrospinal fluid of intrathecal $\beta$-endorphin in monkeys 1984;63:511
Leeds HR. Bacterial filter resistance (correspondence) 1978;57:515
Leeman E, see Hameroff SR
Lees DE, Gadde PL, Macnamara TE. Malignant hyperthermia in association with Burkitt's lymphoma, report of a third case 1980;59:514
  Liquid crystal thermometry (letter) 1979;58:351
  Microwave rewarming (letter) 1980;59:161
  Pierce E, Clements J, Stobie G, Macnamara TE. Computerized audit for anesthesia performance (abstract) 1981;60:262
  Schuette W, Bull JM, Whang-Peng J, Atkinson ER, Macnamara TE. An

evaluation of liquid-crystal thermometry as a screening device for intraoperative hyperthermia 1978;57:669
  see Kim YD
  Shin Y, Macnamara TE. Probable amniotic fluid embolism during curettage for a missed abortion: a case report 1977;56:739
  Vaughan MS, Vaughan RW. Liquid crystal thermometry (letter) 1982;61:803
Lefkowitz M, see Tsueda K
Legrand JJ, see Dupre LJ
Lehmann HD, Kretschmar R. Neuromuscular transmission and verapamil (letter) 1983;62:1048
Lehnert BE, Schachter EN. The pharmacology of respiratory care (book review) 1980;59:895
Lehtinen AM, Fyhrquist F, Kivalo I. The effect of fentanyl on arginine vasopressin and cortisol secretion during anesthesia and surgery 1984;63:25
Leibel WS, Martyn JAJ, Miller KW. Increased *d*-tubocurarine-plasma binding and clinical hyposensitivity following burns trauma (abstract) 1980;59:549
  see Martyn JAJ
Leighton KM, Macleod BA, Bruce C. Renal blood flow: differences in autoregulation during anesthesia with halothane, methoxyflurane or alphaprodine in the dog 1978;57:389
Lekwart FJ, see Hercules PR
Lell WA, see Ingersoll I
  see Posner MA
  see Tosone S
  Walker DR, Blackstone EH, Kouchoukos NT, Allarde R, Roe CR. Evaluation of myocardial damage in patients undergoing coronary artery bypass procedures with halothane-$N_2O$ anesthesia and adjuvants 1977;56:556
Lemoncelli GL, see Fraley DS
Lennon RL, Linstromberg JW. Brachial plexus anesthesia and axillary sheath elastance 1983;62:215
Leon D, see Hirshman CA
Leonard PF. Lower limits of flammability of halothane, enflurane, and isoflurane 1975;54:238
  Nonflammable germicides for detergents (correspondence) 1976;55:606
  see Perry LB
  Use of electrocautery during operation following ether skin prep (questions and answers) 1975;54:210
LeResche L, see Dworkin SF
Lerman J, Gregory GA, Eger EI II. Hematocrit and the solubility of volatile anesthetics 1984;63:911
LeRoy PL. Current concepts in the management of chronic pain "pro dolore" (book review) 1977;56:880
Lescanic AD, see Kistner JR
Lesesne HR, see Campbell RL
Leslie JB, see Bromage P
Lesser ML, see Radnay PA
Letcher J, see El-Naggar M
Letourneau JE, see Denis R
Leung P, see Brower KR
Leventhal JB, see Benzon HT
Levesque PR. Acid-base disorders: application of total body carbon dioxide titration in anesthesia 1975;54:299
  see Rosenberg MB
  Significance with $P_{CO_2}$ within low-pressure endotracheal tube cuffs (brief reports) 1976;55:595
Levin DL, Morriss FC, Moore GC. A practical guide to pediatric intensive care (book review) 1981;60:233
Levin E, Muravchick S, Gold MI. Density of normal cerebrospinal fluid and tetracaine solutions 1981;60:814
  Muravchick S, Gold MI. Isobaric tetracaine spinal anesthesia and the lithotomy position 1981;60:810
Levin JA, see McCullough LS
  see Nigrovic V
Levin KJ, Friedman CP, Scott PV. Anesthesiology and the graduating medical student: a national survey 1979;58:201
  see Campbell RL
  see Gregg JM
Levin RM. Pediatric anaesthesia handbook (book review) 1981;60:172
  Seleny FL, Streczyn MV. Ketamine-pancuronium-narcotic technic for cardiovascular surgery in infants—a comparative study 1975;54:800
Levine H, see El-Naggar M
Levine R, Frost EAM. Arterial blood-gas analyses during electroconvulsive therapy in a parturient 1975;54:203
Levine RJ. Ethics and regulation of clinical research (book review) 1982;61:480
Levinson C, see Hicks JS
Levinson G, see Abboud TK
  see Clarkson CW
  see Rolbin SH
  see Shnider SM
Levitsky S, see Konchigeri HN
Levy JH, Rockoff MA. Anaphylaxis to meperidine 1982;61:301
Levy MN, see Root B
Levy WJ, see Schwartz AJ
Lewis LL. Statistical methods, Student's *t*-test (questions and answers) 1977;56:597
Lewis RE, Cruse JM, Hazelwood J. Halothane-induced suppression of cell-mediated immunity in normal and tumor-bearing $C3H_f$/He mice 1980;59:666
Leysen J, see Stanley TH
L'Hommedieu CS, see Roizen MF
Liang HG, see Liang HS
Liang HS, Liang HG. Minimizing emergence phenomena: subdissociative dosage of ketamine in balanced surgical anesthesia 1975;54:312
Liang JQ, see Colgan FJ
Liarmakopoulou K, see Kaniaris P
Liban BJ. Nasal intubation and a nasogastric tube (letter) 1984;63:166
Lichtenfeld KM, Schiffer CA, Helrich M. Platelet aggregation during and after general anesthesia and surgery 1979;58:293
Lichtenthal PR, Katele G, Holley HS. Unusual case of recovery room air pollution (letter) 1980;59:711
Lichtig C, see Markiewicz W
Lichtiger B, Dupuis JF, Seski J. Hemotherapy during surgery for Jehovah's Witnesses: a new method 1982;61:618
Lichtigfeld FJ, see Gillman MA
Lichtmann MW, see Lee DS
Lichtor JL. Priapism—a therapeutic challenge (letter) 1983;62:1136
  see Friesen RH
  see Myerberg DZ
Lieberman IG, see Matteo RS
Lieberman RW, Whalley DG, Kaplan JA. Indications for pulmonary arterial catheterization (letter) 1982;61:477
Liebeskind JC, see Bonica JJ
Lieding KG, see Waldman J
Light RW, Bengfort JL, George RB. Adult respiratory distress syndrome and pancuronium bromide 1975;54:219
  (correspondence) 1975;54:620
Lilly JK III. An inexpensive portable positive end-expiratory pressure system 1979;58:53
Lim A, see Reitan JA
Lim RA, see Glisson SN
Lim Uy NT, see Abouleish E
Limoge A, see Stanley TH
Lin CY. Assessment of vaporizer performance in low-flow and closed-circuit anesthesia 1980;59:359
  Effect of nitrous oxide solubility on vaporizer aberrance (letter) 1983;62:956
  Enflurane vaporizer accuracy with nitrous oxide mixtures (letter) 1979;58:440
Lina A, see Grundy BL
Lind GL, Spiegel EH, Munson ES.

- Lind GL—*continued*
  - Treatment of traumatic tooth avulsion 1982;61:469
- Linde HW, Mesnick PS, Smith NJ. Causes of death among anesthesiologists: 1930–1946 1981;60:01
  - Oh SO, Homi J et al. Cardiovascular effects of isoflurane and halothane during controlled ventilation in older patients 1975;54:701
  - see Eckenhoff JE
  - Sevoflurane: a new inhalational anesthetic agent (guest discussion) 1975;54:766
- Linder GS. More on wire stylets (correspondence) 1977;56:325
- Lindop AE, see Pflug AE
- Lindquist C, see Rudehill A
- Lineberry C, see Basta SJ
- Lingam RP, see Howie MB
- Lingenfelter AL, Guskiewicz RA, Munson ES. Displacement of right atrial and endotracheal catheters with neck flexion 1978;57:371
- Lingårdh G, see Rawal N
  - Spaeth EE, Wahle WM et al. The influence of suction catheter tip design on tracheobronchial trauma and fluid aspiration efficiency 1976;55:290
- Link WJ, see Dryden GE
- Linke CL, Merin RG. A regional anesthetic approach for renal transplantation 1976;55:69
- Linn PL, see Kuhnert BR
- Linstromberg JW, Muir JJ. Cross-sensitivity in water vapor in the Engström EMMA 1984;63:75
  - see Green CD
  - see Lennon RL
- Lippmann M, Mok MS. Anesthetic management of pulmonary lavage in adults 1977;56:661
  - Mok MS, Steen SN, Harley D, Appel P. Butorphanol as an intravenous adjunct in balanced anesthesia for cardiac surgery (abstract) 1984;63:243
  - Mok MS, Steen SN. Butorphanol anesthesia (letter) 1982;61:624
  - see Reisner LS
  - see Waxman K
  - Yang E, Au E, Lee C. Neuromuscular blocking effects of tobramycin, gentamicin, and cefazolin 200 (abstract) 1982;61:767
- Lipton S, Miles J. Persistent pain: modern methods of treatment, Volume 3 (book review) 1982;61:626
  - Persistent pain: modern methods of treatment (book review) 1978;57:156
  - Relief of pain in clinical practice (book review) 1980;59:637
  - The control of chronic pain, current topics in anaesthesia, Volume 2 (book review) 1980;59:463
- Lisbon A. Anesthetic considerations in setting up a new medical facility: international anesthesiology clinics, Summer, Volume 19 (book review) 1981;60:774
- List WF, Gravenstein JS, Spodick DH. Systolic time intervals (book review) 1980;59:895
- Lister G, see Rothstein P
- Littell L, Kim JM. A simple method for intraoperative blood replacement (brief reports) 1975;54:550
- Littlewood DG, see Armstrong IR
  - see Chambers WA
  - see Ravindran RS
  - see Scott DB
- Litwak RS, see Silvay G
- Litwiller R, see Carron H
- Liu LMP, see Coté CJ
  - see Davies MJ
  - see Goudsouzian NG
- Liu PH. Cardiac arrhythmias (book review) 1984;63:884
- Liu PL, Feldman HS, Covino BM, Giasi R, Covino BG. Acute cardiovascular toxicity of intravenous amide local anesthetics in anesthetized ventilated dogs 1982;61:317
  - Giasi R, Patterson MK, Covino BG. Comparative CNS toxicity of lidocaine, etidocaine, bupivacaine, and tetracaine in awake dogs following rapid intravenous administration 1983;62:375
  - see Desai S
  - see Mallampati SR
  - see Sivarajan M
- Liu PWW, see Fung DL
- Liu WS, Bidwai AV, Stanley TH et al. Cardiovascular dynamics after large doses-of fentanyl and fentanyl plus nitrous oxide in the dog 1976;55:168
  - Petty WC, Jeppsen A, Wade EJ, Pace NL. Attenuation of hemodynamic and hormonal responses to ECT with propranolol, xylocaine, sodium nitroprusside or clonidine (abstract) 1984;63:244
  - see Hill GE
  - see Kawamura R
  - see Sederberg J
  - see Stanley TH
  - Stanley TH, Isern-Amaral J et al. Cardiovascular and respiratory effects of isoproterenol before and after artificial heart implantation 1976;55:560
  - Wong KC, Port JD, Andriano KP. Epinephrine-induced arrhythmias during halothane anesthesia with the addition of nitrous oxide, nitrogen, or helium in dogs 1982;61:414
- Loarie DJ, Fairley HB. Epidural abscess following spinal anesthesia 1978;57:351
  - Wilkinson PL, Tyberg J, White A. The hemodynamic effects of halothane in anemic dogs 1979;58:195
- Lockhart CH, see Zeligs CH
- Loder E, see Tompkins BM
- Loehning RW, see Tanz RD
- Loeschcke HH. Acid base homeostasis of the brain extracellular fluid and the respiratory control system (book review) 1977;56:760
- Loeser EA, Hodges M, Gliedman J, Stanley TH, Johansen RK, Yonetani D. Tracheal pathology following short-term intubation with low- and high-pressure endotracheal tube cuffs 1978;57:577
  - Newman C, Robinson J. Plastic syringes for epidural anesthesia (letter) 1980;59:805
  - Profound hypotension associated with preoperative use of phenothiazines (correspondence) 1975;54:817
  - see Elwyn RA
  - see Hill GE
  - Water-induced resistance in disposable respiratory-circuit bacterial filters 1978;57:269
- Logan MR, see Chambers WA
  - see Ravindran RS
  - see Scott DB
- Logic JR, see Morrow DH
- London CD, Matthews K. Pain control in parturition (correspondence) 1977;56:598
- Londorf D, see Denis R
- Lonergan JG, Zaidan JR, Waller JL, Kaplan JA. Hemodynamics of pacing after aortic valve replacement (abstract) 1981;60:263
- Long MC, see Caplan RA
- Long WB, see Gill W
- Longan M, see Hughes DG
- Longnecker DE. An unusual complication of lumbar puncture: a CSF cutaneous fistula (case history comment) 1975;54:693
  - Case history number 96: reflex sympathetic dystrophy in a 6-year-old: successful treatment by transcutaneous nerve stimulation (comment) 1977;56:441
  - Scientific basis for drug selection 1978;57:603
  - see Bedford RF
  - see Frederickson EL
  - see Kistner JR
- Loop FD, see Estafanous FG
- Lorig JL, see Ernst EA
- Losasso AM, Gosling CG, Sternecker CL, Moorthy SS, Gibbs PS. Adult radial

artery puncture simulator 1978;57:733
  see Gibbs PF
  see Gibbs PS
  see Moorthy SS
Lough MD, Doershuk CF, Stern RC. Pediatric respiratory therapy, second edition (book review) 1980;59:166
  Williams TJ, Rawson JE. Newborn respiratory care (book review) 1981;60:125
Louville Y, see Stanley TH
Love GF, see Moore DC
LoVerne SR, Oropollo AT. Ketamine anesthesia in dermolytic bullous dermatosis (epidermolysis bullosa) 1977;56:398
Loving CD, see Cestone KJ
Lovrien R, see Taylor CA
Low JM, see Prys-Roberts C
Lowe HJ, see Aldrete JA
Lowe HJ, Ernst EA. The quantitative practice of anesthesia, use of closed circuit (book review) 1981;60:849
Lowenstein E, see Nieminen MT
Lower RR, see Rah KH
Lu GW. Neurobiological research on acupuncture in China as exemplified by acupuncture analgesia 1983;62:335
Lubert M, see Root B
Ludden TM, see Lalka D
Luerssen TG, see Ravindran RS
Lukban SB, see Silvay G
Lumley J, Whitwam JG, Morgan M. General anesthesia in the presence of Eisenmenger's syndrome 1977;56:543
Lund PC. Backpain, a contraindication to spinal anesthesia (questions and answers) 1975;54:505
  Heparinization, operative, spinal anesthesia (questions and answers) 1975;54:507
Lundeen G, Manohar M, Parks C. Systemic distribution of blood flow in swine while awake and during 1.0 and 1.5 MAC isoflurane anesthesia with or without 50% nitrous oxide 1983;62:499
Lunn JK, Dannemiller FJ, Stanley TH. Cardiovascular responses to clamping of the aorta during epidural and general anesthesia 1979;58:372
  see Hill GE
  see Stanley TH
  Stanley TH, Eisele J, Webster L, Woodward A. High dose fentanyl anesthesia for coronary artery surgery: plasma fentanyl concentrations and influence of nitrous oxide on cardiovascular responses 1979;58:390
Lunn JN. Lecture notes on anaesthetics (book review) 1979;58:535
Lupo SE, see Bruno LA
Lurz FW, see Cahalan MK
  see Koblin DD
  see Shingu K
Luther RR, see Morrow DH
Lyell H, see Weis OF
Lynch C III. Anesthesia and cardiac performance in health and disease (book review) 1983;62:1139
  Rizor RF. Anesthetic management and monitoring of a parturient with mitral and aortic valvular disease 1982;61:788
Lynch S, see Martis L
Lynch TG, see Vancanti CJ
Lynn AM, see Morray JP
Lyons TE. Preoperative nifedipine management (letter) 1983;62:1138
Lysons DF, see Moore DC
Maass L, see Messick JM
MacDonald AG, Wann KT. Physiological aspects of anaesthetics (book review) 1979;58:536
MacDonell RC Jr, see Parris WCV
MacDonnell KF, Segal MS. Current respiratory care (book review) 1977;56:881
MacEwen GD, see Khine HH
Machida RC, see Katz H
MacKay C, see Ledingham IM
MacKay I, see Koka BV
Mackenzie CF, Ciesla N, Imle PC, Klemic N. Chest physiotherapy in the intensive care unit (book review) 1982;61:481
  Shin B, Hadi F, Imle PC. Changes in total lung/thorax compliance following chest physiotherapy 1980;59:207
  Shin B, McAslan TC. Chest physiotherapy: effect on arterial oxygenation 1978;57:28
MacKenzie RA, see Rorie DK
  see Southorn PA
MacKichan JJ, see Reitz J
Mackie AM, Watson CB. Anesthetic management of mediastinal masses (letter) 1984;63:698
MacKrell TN, see Gould DB
Macleod BA, see Leighton KM
MacLeod SM, see Koren G
MacMahon S, see Feingold A
Macnamara MD, see Park WY
Macnamara TE, see Dubois MY
  see Elsten JL
  see Kareti RKP
  see Kim YD
  see Lee JK
  see Lees DE
  see Park WY
MacVaugh H III, see Conahan TJ III
Madan R, see Kalia PK
Maddi R, see Concepcion M
Maderazo L, see Aleniewski MI
Madhavareddy S, see Rao TLK
Madsen RR, see Carrow DJ
Madura JA, see McCammon RL
  see Stoelting RK
Maduska AL, Guinee WS, Heaton JA et al. Sickling dynamics of red blood cells and other phsyiologic studies during anesthesia 1975;54:361
  Hajghassemali M. Arterial blood gases in mothers and infants during ketamine anesthesia for vaginal delivery 1978;57:121
Maekawa T, see Kaieda R
Magruder MR, see DiFazio CA
Mahaffey JE, see Blackmon BB
  see Dodge TL
  see Hood JB
  see Yakaitis RW
Mahan PE, see Alling CC III
Mahoney E, see Weiskopf RB
Maillé JG, see Boulanger M
Maitra AM, Palmer SK, Bachhuber SR, Abram SE. Continuous epidural analgesia for cesarean section in a patient with morbid obesity 1979;58:348
  see Palmer SK
Maivald P, see Albin MS
  see Newfield P
Maktabi M, see Baraka A
Malagodi MH, see Perry JC
Malina JR, Nordström SG, Sjöstrand UH, Wattwil LM. Clinical evaluation of high-frequency positive-pressure ventilation (HFPPV) in patients scheduled for open-chest surgery 1981;60:324
Maliniak K, Vakil AH. Pre-anesthetic cimetidine and gastric pH 1979;58:309
Malkinson CE, see Atlee JL III
Mallampati SR. Bronchospasm during spinal anesthesia 1981;60:839
  Liu PL, Knapp RM. Convulsions and ventricular tachycardia from bupivacaine with epinephrine: successful resuscitation 1984;63:856
  see Rocco AG
Mallory GB Jr. Control of respiration (book review) 1984;63:627
  Pulmonary function testing guidelines and controversies (book review) 1984;63:707
Mallow JE, White RD, Cucchiara RF et al. Hemodynamic effects of isoflurane and halothane in patients with coronary artery disease 1976;55:135
Malloy WF, Wightman AE, O'Sullivan D, Goldiner PL. Bilateral pneumothorax from suction applied to a ventilator exhaust valve

Malloy WF—*continued*
1979;58:147
Malone BM. A complication of Rusch armored endotracheal tubes 1975;54:756
Maltby JR, see Williams RT
Manawadu BR, Mostow SR, LaForce FM. Impairment of tracheal ring ciliary activity by halothane 1979;58:500
  Mostow SR, LaForce FM. Local anesthetics and tracheal ring ciliary activity 1978;57:448
Manchanda VN, Murad SHN, Shilyansky G, Mehringer M. Unusual clinical course of accidental subdural local anesthetic injection 1983;62:1124
Manchikanti L, Colliver JA, Marrero TC, Roush JR. Ranitidine and metoclopramide for prophylaxis of aspiration pneumonitis in elective surgery 1984;63:903
  Kraus JW, Edds SP. Cimetidine and related drugs in anesthesia 1982;61:595
  Roush JR. Effect of preanesthetic glycopyrrolate and cimetidine on gastric fluid pH and volume in outpatients 1984;63:40
Mandel SD, see Barash P
  see Smith GA
Mangano DT, Hickey RF. Ischemic injury following uncomplicated radial artery catheterization 1979;58:55
  see Bennett MJ
  see Hoar PF
  Ventricular dysfunction following myocardial revascularization (abstract) 1980;59:550
Mangold JV, see Ido Y
Maniscalco JE, see Paul WL
Mankowitz E, see Brock-Utne JG
Mann LI, see Weiss RR
Manninen PH, Nicholas JF, Lam AM. Effects of isoflurane and isoflurane-nitrous oxide anesthesia on brain stem auditory evoked potentials in man (abstract) 1984;63:245
  see Lam AM
Manohar M, see Lundeen G
Manriquez RG, Pallares V. Continuous brachial plexus block for prolonged sympathectomy and control of pain 1978;57:128
Mantena NR, see Wilson SL
Mantia AM. Durability of the Y-piece (letter) 1981;60:912
  Faulty Y-piece (letter) 1981;60:121
  Gas scavenging systems (letter) 1982;61:162
Mao W, see Ghia JN
Mapleson WW, see Mushin WW
Marcy JH. Drugs and anesthesia (book review) 1983;62:127
  The genesis of contemporary American anesthesiology (book review) 1983;62:703
Margand PMS, Brooks CG, Hunter JW. Preoperative pulmonary preparation (book review) 1981;60:698
  Chodoff P. Intermittent mandatory ventilation: an alternative weaning technic: a case report 1975;54:41
Marino RJ, see Burgess GE III
Marios A, see Balamoutsos NG
Maripuu E, see Modig J
Mark JB, Greenberg LM. Intraoperative awareness and hypertensive crisis during high-dose fentanyl-diazepam-oxygen anesthesia 1983;62:698
Mark JBD, see Coe VL
  see Shulman MS
Markand ON, see Moorthy SS
Markello R. Anesthesiology and the law (book review) 1984;63:708
  Complications in anesthesiology (book review) 1984;63:95
  Mortality in anesthesia (book review) 1984;63:787
  see Schuder RJ
Markham JP, see Tang CK
Markiewicz W, Finberg JPM, Lichtig C. Morphine increases myocardial infarction size in rats 1982;61:843
Markowitz AH, see Gerson JI
Marks RG, see Gravenstein JS
Marks WM, see Batra M
Maronic JE, see Ivankovich AD
Maroon J. An unusual complication of lumbar puncture: a CSF cutaneous fistula (case history comment) 1975;54:693
Marques X, Roxas RS. Induction of anesthesia in infant with frontonasal dysplasia and meningoencephalocele: a case report 1977;56:736
Marquez JM. High frequency ventilation (book review) 1984;63:787
  Perspectives in high frequency ventilation (book review) 1984;63:378
  see Martin DJ
Marrero C, see Rafferty TD
Marrero TC, see Manchikanti L
Marrone E, see Priano LL
Marrufo J, see Melman E
Marseglia TJ Jr, see Gabel RA
  see Smith BE
Marsh HM, see Baele PL
Marsh ML, Aidinis SJ, Shapiro HM. Fluctuating intracranial hypertension due to Cheyne–Stokes respiration 1977;56:216
  Dunlop BJ, Shapiro HM, Gagnon RL, Rockoff MA. Succinylcholine-intracranial pressure effects in neurosurgical patients (abstract) 1980;59:550
Marshall BE, see Aukburg SJ
Marshall G, Edelstein G, Hirshman CA. Median nerve compression following radial artery puncture 1980;59:953
Marshall LF, see Shapiro HM
Marshall M. Neuroanesthesia: current topics in anaesthesia, Volume 3 (book review) 1981;60:126
Marshall WK, Bedford RF, Miller ED. Cardiovascular responses in the seated position—impact of four anesthetic techniques 1983;62:648
  Bedford RF, Miller ED. Hemodynamics during anesthesia in the seated position (abstract) 1982;61:201
  Bedford RF, Miller ED Jr. Is morphine-$N_2O$ suitable for the seated position? (letter) 1984;63:169
  see Bedford RF
  see Hagan CH
Martin DE, Rosenberg H, Aukburg SJ, Bartkowski RR, Edwards MWM Jr, Greenhow DE, Klineberg PL. Low-dose fentanyl blunts circulatory responses to tracheal intubation 1982;61:680
  Rosenberg H. Reduction of postintubation hypertension by low dose fentanyl (abstract) 1981;60:264
  see Siedl DC
Martin DJ. Intensive care of the surgical cardiopulmonary patient (book review) 1984;63:379
  Marquez JM, Kant YG, Shaw BW Jr, Pinsky MR. Liver transplantation: hemodynamic and electrolyte changes seen immediately following revascularization (abstract) 1984;63:246
Martin JT. Congenital lobar emphysema (case history) 1976;55:869
  Positioning in anesthesia and surgery (book review) 1979;58:161
  see McCullough LS
  see Nigrovic V
  Venous air embolism prophylaxis with a surface-active agent (guest discussion) 1975;54:798
Martineau R, see Byrick RJ
Martis L, Lynch S, Napoli MD, Woods EF. Biotransformation of sevoflurane in dogs and rats 1981;60:186
Martucci RW, see Reitan JA
Martyn JAJ, Abernethy DR, Greenblatt DJ. Plasma binding of drugs after severe burn injury (abstract) 1984;63:247
  Greenblatt DJ, Quinby WC. Diazepam kinetics in patients with severe burns 1983;62:293

  Leibel WS, Matteo RS. Competitive nonspecific binding does not explain the potentiating effects of muscle relaxants combinations 1983;62:160
  Leibel WS, Matteo RS. Pancuronium and metocurine or *d*-tubocurarine do not compete for the same binding sites in plasma or tissue (abstract) 1982;61:202
  Matteo RS, Greenblatt D, Lebowitz P, Savarese JJ. Comparative pharmacokinetics of *d*-tubocurarine (dTC) in burned and nonburned man (abstract) 1981;60:265
  Matteo RS, Greenblatt DJ, Lebowitz PW, Savarese JJ. Pharmacokinetics of *d*-tubocurarine in patients with thermal injury 1982;61:241
  Matteo RS, Szyfelbein SK, Kaplan RF. Unprecedented resistance to neuromuscular blocking effects of metocurine with persistence after complete recovery in a burned patient 1982;61:614
  see Goudsouzian NG
  see Lebowitz PW
  see Leibel WS
Martz KV, Jointer J, Shepherd RM. Management of the patient-ventilator system, a team approach (book review) 1980;59:83
Martz RC, see Stoelting RK
Maruyama M, see Iwane T
Maruyama Y, see Kaieda R
  see Shimoji K
Marx GF, Bassell GM. Obstetric analgesia and anesthesia, monographs in anaesthesiology, Volume 7 (book review) 1980;59:957
  Clinical management of the mother and newborn (book review) 1980;59:84
  Desai PK, Habib NS. Detection and differentiation of metabolic acidosis in parturients 1980;59:929, (abstract) 1980;59:551
  Hypoventilation in a newborn following administration of succinylcholine to the mother: a case report (comment) 1975;54:39
  see Covino BG
  see Deen SM
  see Gutsche BB
  see Hertz R
  see Hodgkinson R
  see Husain FJ
  see Miclat NN
  see Saka DM
  see Shiau HF
Marx P, see Barash PG
Mashimo T. Rapid warming of stored blood causes formation of bubbles in the intravenous tubing 1980;59:512
Masih AK, see Ramanathan S
Masoud PJ, Ohr JT, Green CD. Transient neurologic changes after epidural morphine (letter) 1981;60:540
Massengale MD, see Park WY
Massey EW. Cluneal neuropathy (correspondence) 1978;57:381
  Pleet AB, Brannon WL. Penicillin neuropathy (letter) 1979;58:63
Mastrokostopoulos GT, see Apostolou GA
Mather LE, see Moore DC
Mathew BP, see Adams HR
Mathieu A, DiPadua D, Kahan BD et al. Correlation between specific immunity to a metabolite of halothane and hepatic lesions after multiple exposures 1975;54:332
Mathru M, Rao TLK, Kartha RK, Shanmugham M, Jacobs HK. Intravenous albumin administration for prevention of spinal hypotension during cesarean section 1980;59:655
Mathur N, see Verma RS
Matloff JM, see Hoffman WE
  see Moffitt EA
  see Sethna DH
Matsubara T, see Clarkson CW
Matsukawa S, see Iwatsuki N
Matsuki A, see Zsigmond EK
Matsuki M, see Iwane T
Matsumoto T. Pre- and postoperative evaluation of surgical patients (book review) 1980;59:228
Matsumoto Y, see Price KA
Matsuo S, Rao DBS, Chaudry I, Foldes FF. Interaction of muscle relaxants and local anesthetics at the neuromuscular junction 1978;57:580
Matteo RS, Lieberman IG, Salanitre E, McDaniel DD, Diaz J. Distribution, elimination, and action of *d*-tubocurarine in neonates, infants, children, and adults 1984;63:799
  see Khambatta HJ
  see Martyn JAJ
Matthews K, see London CD
Matthews MM, see Pace NL
Maturana G, see Urzua J
Matz GJ, see Hassan SZ
Maunuksela EL, Gattiker RI. Use of pancuronium in children with congenital heart disease 1981;60:798
May M, see Barash PG
Mayer BW. Pediatric anesthesia: a guide to its administration (book review) 1981;60:698
Mayer R, see Quintin L
Mayer WD. Evaluation in the continuum of medical education—the GAP report revisited, Baxter-Travenol Lecture (1975) 1975;54:553
Mayhew JF. Difficult spinal taps (letter) 1982;61:309
  Moreno L. Spinal anesthesia for high-risk neonate (letter) 1984;63:782
  Parents in the recovery room (letter) 1983;62:124
  Rudolph J, Tobey RE. Malignant hyperthermia in a six-month-old infant: a case report 1978;57:262
Mays KS, see Schnapp M
Mayumi T, Dohi S. Spinal subarachnoid hematoma after lumbar puncture in a patient receiving antiplatelet therapy 1983;62:777
  Dohi S, Takahashi T. Plasma concentrations of lidocaine associated with cervical, thoracic, and lumbar epidural anesthesia 1983;62:578
  see Dohi S
Mazazan JE, see Chase CR
Maze A, see Samuels SI
Maze M, see Berry AJ
  see Spiss CK
  Smith CM, Baden JM, Land SJ, Mazze RI, Vanderhooft JE. Hepatic function in cirrhotic rats following halothane anesthesia (abstract) 1984;63:248
Mazel P, see Craft JB Jr
Mazuzan JE Jr, see Abajian JC
  see Lambert DH
Mazze RI, see Baden JM
  see Burchiel KJ
  see Cook TL
  see Duvaldestin P
  see Hitt BA
  see Maze M
  see Wharton RS
  see White AE
  Wilson AI, Rice SA, Baden JM. Effects of isoflurane on reproduction and fetal development in mice (abstract) 1984;63:249
  Woodruff RE, Heerdt ME. Isoniazid induces enflurane defluorination in man (abstract) 1982;61:202
McAlpine FS, see Nicholson MJ
McAmis F, see Kim JM
McAslan TC, see Dongre SS
  see Mackenzie CF
McCallum RN, see Gambill AF
McCammon RL, Hilgenberg JC, Stoelting RK. Effect of propranolol on circulatory responses to induction of diazepam-nitrous oxide anesthesia and to endotracheal intubation 1981;60:579, (abstract) 1981;60:265
  Hilgenberg JC, Stoelting RK. Hemodynamic effects of diazepam and diazepam-nitrous oxide in patients with coronary artery disease 1980;59:438, (abstract) 1980;59:551

McCammon RL—*continued*
  see Hilgenberg JC
  see Moorthy SS
  see Stoelting RK
  Stoelting RK, Madura JA. Effects of butorphanol, nalbuphine, and fentanyl on intrabiliary tract dynamics 1984;63:139
McCarthy R, see Braverman B
  see El-Baz N
McCaughey W, see Dundee JW
  see Johnston JR
McClean E, see Johnston JR
McComb RC, see Belani KG
McComb SJ. Visual communication: clarity in lecture slides revisited 1976;55:06
McCord ES. Change in pulmonary venous admixture with varying inspired oxygen (guest discussion) 1976;55:693
McCracken LE Jr, see Reves JG
McCullough JD. Anticoagulants and continuous epidural anesthesia (letter) 1980;59:394
McCullough LS, Nigrovic C, Wajskol A, Levin J, Martin JT. Release of catecholamines by succinylcholine in man (abstract) 1982;61:203
  see Nigrovic V
McCutcheon EP, see Abel FL
McDaniel DD, see Matteo RS
McDermott DJ, see Moss J
McDonnell TE, see Bartkowski RR
McDowell HA, see Gelman S
McElfresh DM. Nifedipine in dogs anesthetized with halothane (letter) 1984;63:622
McGarrigle R, White S. Oxygen analyzers can detect disconnections (letter) 1984;63:464
McGill WA, Coveler LA, Epstein BS. Subacute upper respiratory infection in small children 1979;58:331
McGoldrick KE, Donlon JV. Sublingual hematoma following difficult laryngoscopy 1979;58:343
  Factors influencing development of retrolental fibroplasia (letter) 1981;60:539
McGrath CJ, see Short CE
McGrath PA, see Gracely RH
McKain CW, see Urban BJ
  Urban BJ: Pain and cluneal neuropathy following intragluteal injection 1978;57:138
McKay M, see Ravindran R
McKay RD, Varner PD, Hendricks PL, Adams ML, Harsh GR III. The evaluation of sufentanil-$N_2O$-$O_2$ vs. fentanyl-$N_2O$-$O_2$ anesthesia for craniotomy (abstract) 1984;63:250
McKenzie R, Figallo EM, Tantisira B et al. Anesthesia for jejunoileal shunt: review of 88 cases 1975;54:65
  Management of labor (book review) 1984;63:173
  Wadhwa RK. Obesity supine death syndrome (letter) 1980;59:81
  Wadhwa RK. Progesterone for the Pickwickian syndrome: respiratory implications: a case report 1977;56:133
  Wadhwa RK, Uy NTL, Phitayakorn P, Tantisira B, Sinchioco C, Taylor FH. Antiemetic effectiveness of intramuscular hydroxyzine compared with intramuscular droperidol 1981;60:783
McKlveen JR. Cardiac herniation (correspondence) 1978;57:747
McKnight RL, see Boheler J
McLaren RG, Moffitt EA. Prolonged apnea after succinylcholine in a dental outpatient (case history) 1976;55:737
McLaughlin DF, Eger EI II. Repeated isoflurane anesthesia in a patient with hepatic dysfunction 1984;63:775
McLeskey CH, Boyce WH, Birch AA. Renovascular effects of dopamine in anesthetized man (abstract) 1980;59:552
  Brown EF III, Owens WD, Felts JA. Plasma catecholamine levels (letter) 1982;61:884
  Introducers for 25-gauge spinal needles (letter) 1983;62:1046
  pH of local anesthetic solutions (letter) 1980;59:892
  see Scuderi PE
McMichan JC, see Baele PL
  see Cameron PD
  see Laughlin TP
McNamara PJ, Slaughter RL, Pieper JA, Wyman MG, Lalka D. Factors influencing serum protein binding of lidocaine in humans 1981;60:395
McNay JL, see Lalka D
McNiece WL, see Dierdorf SF
  see Haselby KA
McQuay HJ, see Bullingham RES
  see Watson J
  Weir L, Porter B, O'Sullivan G, Paterson G, Moore A, Bullingham R. A model for comparison of local anesthetics in man 1982;61:418
McQuay HJ, see Cowen MJ
McQueen MJ. Prolonged apnea after succinylcholine in a dental outpatient (case history) (guest discussion) 1976;55:738
McRea JC, see Wong KC
McSherry RT, see Goldberg ME
Means L, see Dierdorf SF
Meere C see Boulanger M
Meguiar RV, Wheeler AS. Lumbar sympathetic block with bupivacaine: analgesia for labor 1978;57:486
Mehrez MP, see Brodsky JB
Mehringer M, see Manchanda VN
Mehta M, see Choi W
Meij S, see Prakash O
Meline LJ, see Westenskow DR
Mellish P, see Abajian JC
Melmann E (correspondence) 1975;54:825
  Penuelas J, Marrufo J. Regional anesthesia in children 1975;54:387
Melmon KL, Morrelli HF. Clinical pharmacology (book review) 1978;57:600
Meltzer HY, Hassan SZ, Russo P et al. Isoenzymes of creatine phosphokinase in serum of families with malignant hyperpyrexia 1976;55:797
  see Moretti RJ
Melzack R. Case history number 96: reflex sympathetic dystrophy in a 6-year-old: successful treatment by transcutaneous nerve stimulation (guest discussion) 1977;56:442
Mendelson G. Reversal of Datura stramonium with physostigmine (correspondence) 1976;55:260
Mendiola J, Grylack LJ, Scanlon JW. Effects of intrapartum maternal glucose infusion on the normal fetus and newborn 1982;61:32
Mendoza C, see Aleniewski MI
Mentelos R, see Rafferty TD
Menzel DB, see Karis JH
Meranze J, Ellison N, Greenhow DE. Publications resulting from anesthesia meeting abstracts 1982;61:445
Meretoja OA, see Nilsson E
Meridy HW, Criteria for selection of ambulatory surgical patients and guidelines for anesthetic management: a retrospective study of 1553 cases 1982;61:921
Merin RG. Calcium blockers—mechanisms of action and clinical applications (book review) 1983;62:542
  Mechanisms of chronotropic effects of volatile inhalation anesthetics (guest discussion) 1977;56:179
  see Linke CL
  see Rogers K
  Terminology and definition of word "metabolism" (questions and answers) 1976;55:760
Merrell RC, see Wyner J
Merrill C, see Yost LC
Merrill DG, Brodsky JB, Hentz RV. Vascular insufficiency following axillary block of the brachial plexus

1981;60:162
  Samuels SI, Silverberg GD. Venous air embolism of uncertain etiology 1982;61:65
Merritt JC, Sprague DH, Merritt WE, Ellis RA. Retrolental fibroplasia: a multifactorial disease 1981;60:109
Merritt WE, see Merritt JC
Merz BA, see Chase CR
Mesnick PS, see Linde HW
Messick JM. Anesthesia and subarachnoid intracranial pressure (guest discussion) 1975;54:498
  Maass L, Faust RJ, Cucchiara RF. Duration of pancuronium neuromuscular blockade in patients taking anticonvulsant medication (abstract) 1982;61:203
  see Warner MA
  Laws ER Jr, Abboud CF. Anesthesia for transsphenoidal surgery of the hypophyseal region 1978;57:206
Mestad PH, see Galvis AG
Metz S, Horrow JC, Balcar I. A controlled comparison of techniques for locating the internal jugular vein using ultrasonography 1984;63:673
Meuleman TR, Port D, Hill D, Pace NL, Stanley TH. Cardiovascular and pulmonary effects of serotonin antagonism before and during endotoxic shock in dogs (abstract) 1982;61:204
Mewaldt SP, see Ghoneim MM
Meyer BH, Weis OF, Müller FO. Antagonism of diazepam by aminophylline in health volunteers 1984;63:900
Meyer JA. Humidity in operating rooms (questions and answers) 1976;55:134
  see Brodsky JB
  see Rendell-Baker L
Meyer RM, Katele GV. The case for a complete Allen's test 1983;62:947
Meyers EF, Muravchick S. Anesthesia induction technics in pediatric patients: a controlled study of behavioral consequences 1977;56:538
  see Chiu TM
  Wilson SL. Vitrectomy: A new challenge for the anesthesiologist 1975;54:58
Meyers MB, Barash PG. Cardiac decompensation during enflurane anesthesia in a patient with myotonia atrophica (case history) 1976;55:433
  Oh TH. Prevention of hypothermia during cystoscopy in neonates (brief reports) 1976;55:592
Meyers SN, see Harrison RA
  see Schoeppel SL
Michaels I, see Sudan NK
  Serrins M, Shier NQ, Barash PG. Anesthesia for cardiac surgery in patients receiving monoamine oxidase inhibitors 1984;63:1041
  Sheehan J. EEG changes due to unsuspected aortic dissection during cardiopulmonary bypass 1984;63:946
Michaels IAL, Barash PG. Hemodynamic changes during protamine administration 1983;62:831
  see Suzukawa M
Michalik R, see Kim YD
Michalk S, see Boulanger M
Michenfelder JD. About throwing stones from glass towers (letter) 1984;63:538
  see Artru AA
Miclat NN, Hodgkinson R, Marx GF. Neonatal gastric pH 1978;57:98
  see Hodgkinson R
Middleton E, see El-Naggar M
Mignogna FV, see Yang JC
Mihm FG, Feeley TW, Downing TP, Sadeghi AM, Baumgartner WA, Reitz BA, Shumway NE. Lung injury after heart-lung transplantation: effects of preservation (abstract) 1984;63:251
  Pulmonary artery pressure monitoring in patients with pheochromocytoma 1983;62:1129
  see Halperin BD
Milde JH, see Gronert GA
Miles J, see Lipton S
Miletich DJ, Ivankovich AD, Albrecht RF et al. Absence of autoregulation of cerebral blood flow during halothane and enflurane anesthesia 1976;55:100
  see Hoffman WE
  see Ivankovich AD
  see Zahed B
  The effects of doxapram on cerebral blood flow and peripheral hemodynamics in the anesthetized and unanesthetized goat 1976;55:279
Milic-Emili J, Aubier M. Some recent advances in the study of the control of breathing in patients with chronic obstructive lung disease 1980;59:865
Millen JE, Glauser FL. Rapid, simple technic for changing endotracheal tubes 1978;57:735
Miller DR, see Pulver JJ
Miller ED, see Delaney TJ
  see Kaplan JA
  see Kistner JR
  see Marshall WK
  see Ritzman JR
  see Woodside JR Jr
Miller EV, see Sivarajan M
Miller F, see Abboud TK
Miller J, see Raj PP
Miller JD, see Conner JT
Miller JM, Cascorbi HF. Yet another vaporizer hazard (letter) 1980;59:805
Miller KW, see Leibel WE
Miller MG, Cullen BF. The cost of scavenging—is it worth it? (editorial) 1979;58:265
  see Cullen BF
Miller MJ. Tissue oxygenation in clinical medicine: an historical review 1982;61:527
Miller MS, see Bentley JB
  see Vaugan RW
Miller R, Boulukos PA, Warner RRP. Failure of halothane and ketamine to alleviate carcinoid syndrome induced bronchospasm during anesthesia 1980;59:621
  see Powell DR
  see Tausk HC
  Tausk HC. Anaphylactoid reaction to vancomycin during anesthesia: a case report 1977;56:870
Miller RD, Anesthesia, Volumes 1 and 2 (book review) 1982;61:165
  Clinical studies involving neostigmine reversal of *d*-tubocurarine, gallamine, and pancuronium in man (correspondence) 1975;54:118
  Filters used during massive blood transfusions (questions and answers) 1975;54:45
  Is atracurium an ideal neuromuscular blocking drug? 1982;61:721
  see Booij LHDJ
  see Cronnelly R
  see Gencarelli PJ
  see Johnston RR
  see Priano LL
  see Smith NT
  see Upton RA
  see Van Nyhuis LS
  see Wilson SL
Miller RN. Neurochemical hypothesis for halothane anesthesia (guest discussion) 1975;54:246
Milliken RA, Bizzarri DV. An unusual cause of failure of anesthetic gas delivery to a patient circuit (letter) 1984;63:1047
  Hazards of scavenging systems (letter) 1980;59:162
  Humidification of anesthesia gases (letter) 1981;60:694
  see Jove F
  see Rendell-Baker L
Mills J, see Mathieu A
Milne B, see Rooke NT
Milocco I, see Pontén J
Milstein J, Rabinovitz J, Goetzman B. A foreign-body hazard in the neonate 1977;56:726

- Mindlin LJ, see Wallace G
- Minuck M, Sharma GP. Comparison of THAM and sodium bicarbonate in resuscitation of the heart after ventricular fibrillation in dogs 1977;56:38
- Mirakhur RK, Dundee JW. Gastric acidity and glycopyrrolate premedication (letter) 1979;58:157
  - Dundee JW, Jones CJ, Coppel DL, Clarke RSJ. Reversal of neuromuscular blockade: dose determination studies with atropine and glycopyrrolate given before or in a mixture with neostigmine 1981;60:557
  - Pandit SK, Ferres CJ, Gibson FM. Statistically significant differences vs clinically significant differences (letter) 1984;63:1050
  - Pandit SK, Ferres CJ, Gibson FM. Time course of muscle relaxation with a combination of pancuronium and tubocurarine 1984;63:437
  - see Pandit SK
- Mishima S, Yamamura T. Anaphylactoid reaction to pancuronium 1984;63:865
- Misle GR, see Safwat AM
- Mitchell FL, see Brown SS
- Mitchell G, Heffron JJA. Malignant hyperthermia (letter) 1980;59:891
  - Heffron JJA, van Rensburg AJJ. A halothane-induced biochemical defect in muscle of normal and malignant hyperthermia-susceptible Landrace pigs 1980;59:250
  - see Heffron JJA
- Mitchell SA, Shoults DL, Herren AL, Benumof JL. Deglutition of an endotracheal tube: a case report 1978;57:590
- Mitzner W, see Ngeow YK
- Modell JH. Intermittent mandatory ventilation in the treatment of patients with chronic obstructive pulmonary disease (correspondence) 1975;54:119
  - Lee PKY, Bingham HG et al. "Acupuncture anesthesia"—a clinical study 1976;55:508
  - see Barasch ST
  - see Cottrell WM
  - see James CF
  - see Lee PKY
  - see Nimocks JA
  - see Perschau RA
  - see Pyles ST
- Modig J, Borg T, Karlström G, Maripuu E, Sahlestedt B. Thromboembolism after total hip replacement: role of epidural and general anesthesia 1983;62:174
- Mody BB, see Samsi AB
- Moffitt EA. Anesthesia for patients early after infarction 1976;55:640
  - Anesthesia for the patient with cardiac disease: preamble 1976;55:617
  - Barker RA, Glenn JJ, Imrie DD, Delcampo C, Landymore R, Kinley CE, Murphy DA. Myocardial metabolism and hemodynamic responses with isoflurane anesthesia for coronary artery surgery (abstract) 1984;63:252
  - Emergency operation during acute myocardial infarction (case history comment) 1975;54:268
  - Prolonged apnea after succinylcholine in a dental outpatient (case history comment) 1976;55:738
  - Scovil JE, Imrie DD, Glenn JJ, Cousins CL, Sullivan JA, Kinley CE. The effects of nitrous oxide on myocardial metabolism and hemodynamics during fentanyl or enflurane anesthesia in patients with coronary disease 1984;63:1071
  - see Isac F
  - see McLaren RG
  - see Sethna DH
  - Sethna D, Bussell J, Raymond M, Matloff J, Gray R. Hemodynamics and myocardial metabolism after acute β-adrenergic blockade in coronary patients (letter) 1984;63:540
  - Sethna D, Gray R, DeRobertis M, Bussell J, Matloff J. Rate-pressure product correlates poorly with $MVO_2$ during anesthesia in coronary patients (abstract) 1982;61:204
  - Sethna D, Gray R, Matloff J, Bussell J, Coronary blood flow, $MO_2$, and hemodynamics during halothane and morphine anesthesia for coronary artery surgery (abstract) 1981;60:266
  - Sethna DH, Bussell JA, Raymond M, Matloff JM, Gray RJ. Myocardial metabolism and hemodynamic responses to halothane or morphine anesthesia for coronary artery surgery 1982;61:979
  - Tarhan S, Rodriguez R et al. Hemodynamic effects of morphine during and early after cardiac operations 1976;55:47
- Mogelnicki S. Role of lithium in clinical anesthesiology (questions and answers) 1977;56:462
- Mogensen T, see Hasselstrøm LJ
- Mogos B, Phillips P, Apfelbaum R, Duncalf D. Is right atrial catheterization always indicated for anesthesia in the sitting position? (abstract) 1982;61:205
- Mohindra P, see Saleh-Shenaq S
- Moir DD. Obstetric anaesthesia and analgesia (book review) 1977;56:759
- Mok MS, see Lippmann M
- Moldenhauer CC, Hug CC. Continuous infusion of fentanyl for cardiac surgery (abstract) 1982;61:206
  - see Murkin JM
  - see Welti RS
- Moles M, see Norman J
- Molitch ME. Management of medical problems in surgical patients (book review) 1982;61:1027
- Möllefors K, see Rawal N
- Molloy RE, see Benzon HT
- Momnet Y, see Etchia A
- Moncorge C, see Vourc'h G
- Mondino M, see Craft JB Jr
- Monies-Chass I, Bar-Maor JA, Shoshany G. Cimetidine and congenital tracheoesophageal fistula (letter) 1983;62:620
- Montoya A, see Mummaneni N
- Moon BJ, see Geha DG
- Moon GJ. Pericardial effusion and severe tachycardia 1982;61:384
- Moore A, see Bullingham R
  - see Cowen MJ
  - see McQuay H
  - see Watson J
- Moore D, see Wyrobek AJ
- Moore DC, Bridenbaugh LD, Thompson GE, Balfour RI, Horton WG. Bupivacaine: review of 11,080 cases 1978;57:42
  - Bridenbaugh PO, Bridenbaugh LD et al. Bupivacaine compared with etidocaine for vaginal delivery 1975;54:250
  - Bush WH, Burnett LL. Celiac plexus block: a roentgenographic, anatomic study of technique and spread of solution in patients and corpses 1981;60:369
  - Bush WH, Scurlock JE. Intercostal nerve block, a roentgenographic anatomic study of technique and absorption in humans 1980;59:815, (abstract) 1980;59:553
  - Chloroprocaine not absolved of neurotoxicity (letter) 1984;63:544
  - Mather LE, Bridenbaugh LD et al. Arterial and venous plasma levels of bupivacaine following peripheral nerve blocks 1976;55:763
  - Scurlock JE. Possible role of epinephrine in prevention or correction of myocardial depression associated with bupivacaine 1981;60:450
  - see Riggi SJ
  - see Thompson GE
  - Spierdijik J, vanKleef JD, Coleman RL, Love GF. Chloroprocaine

neurotoxicity: four additional cases 1982;61:155
  Spinal anesthesia, bupivacaine compared with tetracaine 1980;59:743
  The pH of local anesthetic solutions 1981;60:833
Moore EB. Attorney urges study of doctors' professional relationships (editor's choice) 1976;55:756
Moore GC, see Levin DL
Moore J, see Dundee JW
  see Johnston JR
Moore KP. Cannulation of the dorsal radial artery (letter) 1983;62:540
Moore PA, Burney RG. Analgesic properties of lidocaine in mice 1979;58:85
  see Korevaar WC
Moore RA, Geller EA, Clark DL. Superficial cervical plexus damage as a result of a back roll 1982;61:471
  see Gallagher JD
Moore WE, Watson RL, Summary JJ. Massive myoglobinuria precipitated by halothane and succinylcholine in a member of a family with elevation of serum creatine phosphokinase 1976;55:680
Moore WH, see Campbell RL
Moorehead MT, Westengard JC, Bull BS. Platelet involvement in the activated coagulation time of heparinized blood 1984;63:394
Moorthy SS. Cannulation of the anterior peroneal artery in adults 1981;60:360
  Franken EA, LoSasso AM et al. Respiratory distress with left aortic arch, right descending aorta, and right ligamentum arteriosum: a case report 1976;55:481
  Hilgenberg JC. Resistance to non-depolarizing muscle relaxants in paretic upper extremities of patients with residual hemiplegia 1980;59:624
  LoSasso AM, King H et al. Evaluation of larynx and trachea by xeroradiography (brief reports) 1976;55:598
  Markand ON, Dilley RS, McCammon RI, Warren CH Jr. Somatosensory-evoked responses during carotid end-arterectomy 1982;61:879
  Pond W, Rowland RG. Severe circulatory shock following protamine (an anaphylactic reaction) 1980;59:77
  Reddy RV, Paradise RR, LoSasso AM, Gibbs PS. Reduction of enflurane-induced spike activity by scopolamine 1980;59:417
  see Gibbs PS
  see LoSasso AM
  see Wagner DL
Moran S, see Urzua M
Moravec MA, Hurlbert BJ. Hypokalemia associated with terbutaline administration in obstetrical patients 1980;59:917
Morel D, see Forster A
Moreland JR, see Saucier N
Morell F, see Ford EW
Moreno L, see Mayhew JF
Moretti RJ, Hassan SZ, Goodman LI, Meltzer HY. Comparison of ketamine and thiopental in healthy volunteers: effects on mental status, mood, and personality 1984;63:1087
Morgan LS, see Berger JJ
Morgan M, see Lumley J
Morgan QL, see Neuman GG
Mori K, see Harioka T
Morin JE, see Quintin L
Morioka T, see Juang MS
Morishima HO, see Pedersen H
Morison DH, Dunn GL, Fargas-Babjak AM, Moudgil GC, Smedstad K, Woo J. A double-blind comparison of cimetidine and ranitidine as prophylaxis against gastric aspiration syndrome 1982;61:988
Morissette M, see Hardy JF
Morita S, Latta W, Hambro K, Snider MT. Accumulation of methane, acetone, and nitrogen in the inspired gas during closed circuit anesthesia (abstract) 1981;60:267
Morray JP, Brandford HG, Barnes LF, Oh SM, Furman EB. Doppler-assisted radial artery cannulation in infants and children 1984;63:346
  Lynn AM, Stamm SJ, Herndon PS, Kawabori I, Stevenson JG. Hemodynamic effects of ketamine in children with congenital heart disease 1984;63:895
Morrelli HF, see Melmon KL
Morris L, see Bedford RF
Morris PJ, see Todd MM
Morris RB, see Cronnelly R
Morrison JA, see Warren TM
Morriss FC, see Levin DL
Morrissette M, see Hardy JF
Morrow DH. Cardiac decompensation during enflurane anesthesia in a patient with myotonia atrophica (case history comment) 1976;55:436
  Halothane effects on conductivity of the AV node and His-Purkinje system in the dog (guest discussion) 1977;56:378
  Intravenous potassium chloride in hypokalemic dogs pretreated with digoxin (guest discussion) 1978;57:113
  Logic JR, Haley JV. Antiarrhythmic anesthetic action. I. The effect of halothane on canine intracardiac impulse conduction during sinus rhythm 1977;56:187
  Luther RR. Anaphylaxis: etiology and guidelines for management 1976;55:493
  see Fox F
  see Saleh SA
  see Warren JE
Morrow JG III. Allergy to succinylcholine (letter) 1981;60:456
Mortara D, see Kotrly KJ
Morton AW. Technic of medullary narcosis (editor's choice) 1975;54:579
Moscicki JC, see DiFazio CA
  see Hecker BR
  see Rowlingson JC
Moshal MG, see Brock-Utne JG
Moss J, McDermott DJ, Thisted RA, Roizen MF, Smith WS. Anaphylactic/anaphylactoid reactions in response to chymodiactin (chymopapain) (abstract) 1984;63:253
  see Kono K
  see Philbin DM
  see Todd MM
  see Tomichek RC
Moss P, see Ramanathan S
Mosteller F, see Bunker JP
Mostert JW. Spontaneous extubation (case report) 1977;56:293
Mostow SR, LaForce FM. Pulmonary antibacterial defense mechanisms are depressed by halothane 1979;58:505
  see Manawadu BR
Motomura S, Kissin I, Aultman DF, Reves JG. Effects of fentanyl and nitrous oxide on contractility of blood-perfused papillary muscle of the dog 1984;63:47
  see Kissin I
Motoyama EK. Pulmonary physiology (book review) 1983;62:374
Moudgil GC, see Morison DH
Moumdjian J, see Abboud TK
Mouradian E, see Baraka A
Moustapha I, see Corssen G
Mowbray AG, see Hicks HC
Moya F, see Lichtiger M
Moyers JR, see Bastard OG
  see Comstock MK
  see Pochanapring A
  see Wilkinson PL
Moyes DG, see Vieira E
Muallem M, see Baraka A
Mueller RA, see Ghia JN
Muir JJ, see Linstromberg JW
Muldoon S, Otto J, Freas W, Watson RL. The effects of morphine,

Muldoon S—*continued*
nalbuphine, and butorphanol on adrenergic function in canine saphenous veins 1983;62:21
Muldoon SM. Preoperative blood volume determination (questions and answers) 1976;55:275
see Landmark SJ
see Rorie DK
Müller FO, Weis OF. Management of cholinesterase poisoning in obstetrics (letter) 1983;62:1156
see Meyer BH
see Weis OF
Muller J, see Ravindran RS
Mulroy MF, Coombs JHB, Isenberg MD, Fairley HB. Age, chronic obstructive pulmonary disease, and Innovar-induced ventilatory depression during regional anesthesia 1977;56:826
see Sivarajan M
Mulvehill J, see Koht A
Mummaneni N, Rao TLK, Montoya A. Awareness and recall with high-dose fentanyl-oxygen anesthesia 1980;59:948
see Rao TLK
Munch DR, see Stiff JL
Munro I, see Fisher MMcD
Munson ES. Cardiac decompensation during enflurane anesthesia in a patient with myotonia atrophica (case history comment) 1976;55:435
Deaths from local anesthetics (letter) 1980;59:955
Eger EI II, Tham MK, Embro WJ. Increase in anesthetic uptake, excretion, and blood solubility in man after eating 1978;57:224
Hoffman JC, Eger EI II. Use of cyclopropane to test generality of anesthetic requirement in the elderly 1984;63:998
Lee R, Kushins LG. A new complication associated with the use of wire-reinforced endotracheal tubes 1979;58:152
Rediscovering the larynx (letter) 1983;62:855
see Ausinsch B
see Garcia-Bengochea F
see Gibbs CR
see Heard SO
see Lind GL
see Lingenfelter AL
see Paul WL
see Perry JC
see Pyles ST
see Williamson DC III
Murad SHN, Conklin KA
Tabsh KMA, Brinkman CR III, Erkkola R, Nuwayhid B. Atropine and glycopyrrolate: hemodynamic effects and placental transfer in the pregnant ewe 1981;60:710
see Manchanda VN
Murakawa T, see Fukuda S
Muravchick S, Owens WD. An unusual complication of lumbosacral plexus block: a case report 1976;55:350
see Gold MI
see Levin E
see Meyers EF
Murkin JM. Anesthesia and hypothyroidism: a review of thyroxine physiology, pharmacology, and anesthetic implications 1982;61:371
Moldenhauer CC, Hug CC Jr, Epstein CM. Absence of seizures during induction of anesthesia with high-dose fentanyl 1984;63:489
Murphy DA, see Moffitt EA
Murphy ME, see Eyler SW
Murphy TM, see Pflug AE
Murray AL, see Katz RL
see Stirt JA
Murray E, see Concepcion M
Murray GF, see Brown DR
Mushin WW, Rendell-Baker L, Thompson PW, Mapleson WW. Automatic ventilatiton of the lungs, third edition (book review) 1980;59:522
Mutch WAC, Culligan JD, Cote DD, Thomson IR. Hemodynamic effects of intravenous nitroglycerin: importance of the delivery system 1982;61:927
Myerberg DZ, Krall JM, Friesen RH, Lichtor JL. Blood pressure measurements in infants (letter) 1982;61:956
Myers JA, see Denson DD
Myers ML, see Dickinson GE
Myhre BA, Bove JR, Schmidt PJ. Wrong blood—a needless cause of surgical deaths 1981;60:777
Nadel JA. Physiology and pharmacology of the airways (book review) 1981;60:171
Nadkarni AV, Tondare AS. Epinephrine and systemic local toxicity (letter) 1984;63:702
Tondare AS, Localized clonic convulsions after spinal anesthesia with lidocaine and epinephrine 1982;61:945
Nagappala S, see Abboud TK
Nagashima H, see Amaki Y
see Duncalf D
see Foldes FF
see Shiraku Y
Stoll M, Nguyen H, Duncalf D, Foldes F. Surgical relaxation with metocurine-pancuronium combinations (abstract) 1984;63:254
Nagel EL, see Lee C
Nagle DM, see Waller JL
Nahrwold ML, see Denlinger JK
see Jones RM
see Knight PR
Naidu R, see Khine HH
Naiem H, see James FM III
Naik N, see Lee K
Najak Z, see Hammonds W
Nakajo M, see Weinberg S
Nakamura T, see Fujita T
Nance P, see Chapin JW
see Peters KR
Napoli MD, see Martis L
see Wallin RF
Nardi D, see Rafferty TD
Narkham JP, see Chalon J
Nash CL Jr, see Pathak KS
Nasser JG, see Polta TA
Nathan H, see Sprigge JS
Nathanson HG, see Weiss RR
Naulty JS, Herold R. Successful epidural anesthesia following epidural blood patch 1978;57:272
Reves JG, Tobey RE, Schultz WW. Hepatitis and operating-room personnel: an approach to diagnosis and management 1977;56:366
see Datta S
see Steinbrook RA
see Warren TM
Nauss LA, see Faust RJ
see Ward EM
Nauta J, de Lange S, Koopman D, Spierdijk J, van Kleef J, Stanley TH. Anesthetic induction with alfentanil: a new short-acting narcotic analgesic 1982;61:267
see Prakash O
Nawaf K, see Stoelting RK
Stoelting RK. Nitrous oxide increases enflurane concentrations delivered by Ethrane vaporizers 1979;58:30
Neidzwski JT, see Wald A
Neilsen NC, Rusy BF. Effect of nitroprusside on directly measured myocardial $O_2$ consumption during halothane anesthesia (abstract) 1980;59:554
Nelson DO, see Rorie DK
Nelson LR, see Popp AJ
Nelson NT, see Hoar PF
see Koblin DD
Nelson OL, see Lawson NW
Nelson TE, Flewellen EH, Gloyna DF. Spectrum of susceptibility to malignant hyperthermia—diagnostic dilemma 1983;62:545
Flewellen EH, Gloyna DF. Susceptibility of malignant hyperthermia (letter) 1984;63:91
Malignant hyperthermia (letter) 1980;59:890
see Flewellen EH

Nematzadeh D, see Kim YD
Nenad RE Jr, see Bentley JB
Nerothin DD, Kane PF. Calcium—vasodilator or vasoconstrictor? (abstract) 1984;63:255
Neufeld GR, see Aukburg SJ
Neuman GG, Asher AS, Stern SB, Wenig BL, Morgan QL. High-frequency jet ventilation for tracheal resection in a child 1984;63:1039
Neuvonen P, see Nilsson E
Nevelsteen M, see d'Hollander AA
Newbower RS, see Gravenstein JS
Newfield P, Chestnut JS, Maivald P, Pautler S, Albin MS. Nitroprusside and cerebral blood flow (correspondence) 1978;57:142
Newland M, see Chapin JW
Newland MC, Hurlbert BJ. Chemodectoma diagnosed by hypertension and tachycardia during anesthesia 1980;59:388
Newman C, see Loeser EA
Newman T, Franssen R. Uvular edema in pediatric patients (letter) 1984;63:701
Newmark Z, see Ravin M
Newsome L, Bramwell RS. Severe preeclampsia—hemodynamic effects of lumbar epidural anesthesia (abstract) 1984;63:256
Ng TY, Datta TD. Difficult extubation of an endotracheal tube cuff (brief reports) 1976;55:876
  Kirimli BI. Hazards in use of anode endotracheal tube: a case report and review 1975;54:710
Ngeow YF, see Rafferty TD
Ngeow YK, Mitzner W. Gas exchange and high frequency ventilation (letter) 1981;60:363
Nguyen H, see Nagashima H
Nguyen L, see Cronnelly R
Nguyen TL, see Upton RA
Nicholas JF, see Lam AM
  see Manninen PH
Nicholson JA, Sada T, Aldrete JA. Residual halothane: patient and personnel exposure 1975;54:449
Nicholson MJ, McAlpine FS. Method to identify a cervical esophageal diverticulum during general anesthesia (correspondence) 1976;55:893
  Nonflammable fires in the operating room (case history comment) 1975;54:152
  Plastic-covered solid copper wire stylet (brief reports) 1976;55:150
  Plastic-covered wire stylet (correspondence) 1976;55:755
  Respiratory obstruction associated with induction of general anesthesia in a patient with mediastinal Hodgkin's disease (case history comment) 1985;54:402
Nicholson SA, see Brown CQ
Niebauer MJ, see Ralston SH
Niederlehner JR, Berry FA Jr. Transfusion anemia 1979;58:439
  see DiFazio CA
Niejadlik K, Galindo A. Electrocorticographic seizure activity during enflurane anesthesia 1975;54:722
Nielsen CH, see Bromage PR
  see Camporesi EM
Nielsen NC, Rusy BF. Effect of sodium nitroprusside on directly measured myocardial oxygen consumption during phenylephrine-induced hypertension in dogs anesthetized with halothane 1980;59:835
Niemegeers CJE, see Stanley TH
Nieminen MT, Rosow CE, Triantafillou A, Schneider RC, Lowenstein E, Philbin DM. Temperature gradients in cardiac surgical patients—a comparison of halothane and fentanyl 1983;62:1002
Nigrovic C, see McCullough LS
Nigrovic V, McCullough LS, Wajskol A, Levin JA, Martin JT. Succinylcholine-induced increases in plasma catecholamine levels in humans 1983;62:627
  Succinylcholine-induced increases in plasma catecholamine levels in humans (letter) 1984;63:465
Nilsson E, Meretoja OA, Neuvonen P. Hemodynamic responses to physostigmine in patients with a drug overdose 1983;62:885
Nimocks JA, Modell JH, Perry PA. Carbon dioxide retention using a humidified "nonrebreathing" system (brief reports) 1975;54:271, (correspondence) 1975;54:618
Nio K, see Kikuchi H
Nishimura K, see Tatekawa S
  see Yukioka H
Nivoche Y, see Duvaldestin P
Noback CR. Isoflurane versus enflurane in aortic stenosis (abstract) 1982;61:206
Noble WH, see Byrick RJ
Noe FE, Whitty AJ, Davies KR, Wickham BL. Noninvasive measurement of pulmonary gas exchange during general anesthesia 1980;59:263
Nolan NG, see Landmark SJ
Nolan SP. Cardiovascular effects of minimal analgesic quantities of Innovar, fentanyl, and droperidol in man (guest discussion) 1975;54:22
  see Lake CL
Nooh NG, see Salhab AS
Noonan AF, see Tompkins BM
Nordin U, see Klain M
Nordström L, Fletcher R. Comparison of two different J-wires for central venous cannulation via the external jugular vein 1983;62:365
Nordström SG, see Malina JR
Norel E, see Kapur PA
Norfleet EA, see Bazaral MG
  see Friedman GA
  see Saltzman LS
  see Sprague DH
Norman J, Moles M. Management of the injured patient, (book review) 1979;58:355
Normana E, see Sosis M
North AF, see Sawhney KK
North WC, see Maduska AL
  see Schnapp M
Norton AC, see Bachman TE
Norton M, see Hughes SC
  see Rosen MA
Norton ML, see Snow JC
Norway SB, see Sage DJ
Norwood WI, see Hickey PR
Nottingham PB, see Bodai BI
Noueihed R, see Abboud TK
  see Baraka A
Novack GD, Ursillo RC. Malfunctioning halothane vaporizer (letter) 1981;60:121
Novakovic M, see Radnay PA
Nunn JF. Applied respiratory physiology, second edition (book review) 1980;59:85
  see Gray TC
Nuwayhid B, see Murad SHN
Nydahl PA, see Rawal N
Nyhman H, see Bålfors E
Obara S, see Iwatsuki K
O'Brien JE, see Weiss R
Ochs HR, see Divoll M
Ochsner JL, see Diaz JH
O'Connor B, see Koblin DD
O'Connor ME, see Goldberg ME
Odgers CL, see Phillips GD
Odoom JA, Sih IL. Respiratory depression after intrathecal morphine (letter) 1982;61:70
Offord KP, see Southorn PA
O'Gara JP, Edelman JD. Anesthesia and the patient with complete congenital heart block 1981;60:906
Ogawa S, Fink BR, Cairns AM. Differential vulnerability of large and small mammalian myelinated fibers to glucose lack 1984;63:15
Oguchi K, see Ueda I
Oh SM, see Morray JP
Oh SO, see Linde HW
Oh TE. Intensive care manual (book review) 1981;60:915
Oh TH, see Meyers MB
Ohlweiler DF, see Denson DD

Ohmura A, see Hathaway BN
  see Pace NL
  see Wong KC
Ohn K-C, Wu WH. Another complication of armored endotracheal tubes 1980;59:215
Ohr JT, see Masoud PJ
Oikkonen MP, see Rosenberg PH
O'Kafo BA, see Baxter AD
Okuda Y, see Sari A
Olewine SK, see Fukunaga AF
  see Flacke JW
  see Kapur PA
Oliverio RM Jr, Fermon C, Abramowitz R. Periodic apnea during adenotonsillectomy 1979;58:50
  see Ehrenpreis MB
Olsen D, see Stanley TH
O'Meara JB, Chalon J, Amirdivani M, Ali M, Day M, Turndorf H. Tracheobronchial cytologic changes and abnormal serum electrophoretic pattern during induced hypotension 1980;59:197
  see Capan L
Ominsky AJ. Role of lithium in clinical anesthesiology (questions and answers) 1977;56:463
  see Garber JG
  see Schwartz AJ
Ona FV, Patanella H, Ayub A. Hepatitis associated with enflurane anesthesia 1980;59:146
O'Neal F, see Karis JH
O'Neill J, see Giffin JP
Ong BY, see Gregory GA
Ono K, see Foldes FF
Onofrio BM, see Gronert GA
Oparil S, see Reves JG
  see Shepard LS
O'Reily LP, see Kondo K
Orkin FK, see Garber JG
  see Rosenberg H
  see Schwartz AJ
  The quality of care in anesthesia (book review) 1983;62:243
Orkin LR, see Stanec A
Orko RH, see Rosenberg PH
Oropollo AT, see LoVerme Sr
Orr R. Reversal of datura stramonium delirium with physostigmine: report of three cases 1975;54:158
Orr RA. Respiratory monitoring in intensive care (book review) 1984;63:171
Orsine L, see Kaplan RF
Östelius J, see Rawal N
Ostheimer G, see Brunner EA
Ostheimer GW. A comparison of glycopyrrolate and atropine during reversal of nondepolarizing neuromuscular block with neostigmine 1977;56:182
  see Datta S
  see Warren TM
O'Sullivan D, see Malloy WF
  see Vuckovic DD
O'Sullivan GM, Bullingham RE. Does twice the volume of antacid have twice the effect in pregnant women at term? 1984;63:752
  Bullingham RES. Radio pills for measurement of duration of action of sodium citrate (letter) 1983;62:368
  see Bullingham RES
  see McQuay H
Ota MK, see Roizen MF
Otcasek D, see Goudsouzian NG
Ott M, see Salts L
Otto CW, Quan SF, Conahan TJ, Caulkins JM, Waterson CK, Hameroff SR. Hemodynamic effects of high-frequency jet ventilation 1983;62:298
  see Blitt CD
  see Mulcoon S
  see Waterson CK
Ovassapian A, see Benzon HT
  Yelich SJ, Dykes MHM, Brunner EE. Fiberoptic nasotracheal intubation—incidence and causes of failure 1983;62:692, 951
Overbeek J, see Sia RL
Owens WD, Gustave F, Sclaroff A. Tympanic membrane rupture with nitrous oxide anesthesia 1978;57:283
  International anesthesiology clinics: anesthetic side effects and complications: seeking, finding, and treating (book review) 1981;60:126
  see Brown FF III
  see McLeskey CH
  see Muravchick S
  Waldbaum LS, Stephen CR. Cardiac dysrhythmia following reversal of neuromuscular blocking agents in geriatric patients 1978;57:186
  Zeitlin CL. Hypoventilation in a newborn following administration of succinylcholine to the mother: a case report 1975;54:38
Oxorn D. Postpartum deterioration in the presence of valvular heart disease (letter) 1983;62:460
Ozaki GT, see Benumof JL
  see Ward CF
Ozdil T, von der Lage FC Jr, Kattine AA, Duncan OJ. Postintubation acute respiratory distress due to annular slough of laryngotracheal mucosa 1977;56:356
Pace JB. Pulmonary vascular response to sodium nitroprusside in anesthetized dogs 1978;57:551
Pace NL. Fluctuating hypoxemia and pulmonary shunting following fatal head trauma: a case report 1977;56:129
  Hemodynamic calculations (letter) 1980;59:519
  Matthews MM, Stanley TH. Anesthetic management of the first permanent, orthotopic, prosthetic cardiac replacement (total artificial heart) in man 1984;63:685
  Ohmura A, Wong KC. Epinephrine-induced arrhythmias: effect of exogenous prostaglandins and prostaglandin synthesis inhibition during halothane-$O_2$ anesthesia in the dog 1979;58:401
  see Andriano KP
  see Bailey PL
  see Liu WS
  see Meuleman TR
  see Stanley TH
  see Westenskow DR
  Westenskow DR, East TD, Jordon WS. Differential lung ventilation following unilateral hydrochloric acid aspiration in the dog (abstract) 1982;61:207
  Wong KC. Failure of naloxone and naltrexone to antagonize halothane anesthesia in the dog 1979;58:36
Paddleford RR, see Short CE
Padilla LM, see Ravindran R
Paegle RD, Bernhard WN. Squamous metaplasia of tracheal epithelium associated with high volume, low pressure airway cuffs 1975;54:340
  Bernhard WN, Turndorf H. Intermittent exposure to 40 percent oxygen prolongs rat survival in 100 percent oxygen 1977;56:847
  Kiefer L. Request the organizers of national medical meetings to use a speaker's performance index (correspondence) 1977;56:750
Pagano RR, see Conner JT
  see Graham CW
Palacios I, see Landry LD
Palahnuik RJ, Doig GA, Johnson GN, Pash MP. Maternal halothane anesthesia reduces cerebral blood flow in the acidotic sheep fetus 1980;59:35
  see Kozody R
Palazzo M, Williams RT. Blood pressure and heart rate changes during fiberoptic nasotracheal intubation (letter) 1984;63:623
Palermo LM, Andrews RW, Ellison N. Avoidance of heparin contamination in coagulation studies drawn from indwelling lines 1980;59:222
  see Schwartz AJ
Pallares V, see Manriquez RG
Palm T, Husum B. Blood pressure in the great toe with simulated occlusion of the dorsalis pedis artery

1978;57:453
Palmer SK, Abram SE, Maitra AM, von Colditz JH. Distance from the skin to the lumbar epidural space in an obstetric population 1983;62:944
  Bosnjak ZJ, Hopp FA, von Colditz JH, Kampine JP. Lidocaine and bupivacaine differential blockade of isolated canine nerves 1983;62:754
  Maitra AM, Jahn EP, Abram SE. Obstetric side brace for the delivery room table (letter) 1984;63:1046
  see Maitra AM
  see Patel KD
Palti Y, see Bitterman H
Pan P, see Abouleish EI
Pan TH, Wollack AR, DeMarco JA. Malignant hyperthermia associated with enflurane anesthesia: a case report 1975;54:47
Pandit SK, Kothary SP, Pandit UA, Mirakhur RK. Combination of cimetidine and metoclopramide to prevent acid aspiration (abstract) 1984;63:257
  Mirakhur RK, Ferres C, Gibson F. Time course of muscle relaxation with a combination of pancuronium and tubocurarine (abstract) 1984;63:258
  see Kumar N
  see Kumar SM
  see Mirakhur RK
  see Pandit UA
Fandit UA, Kothary SP, Samra SK, Domino EF, Pandit SK. Physostigmine fails to reverse clinical, psychomotor, or EEG effects of lorazepam 1983;62:679
  see Jones RM
  see Pandit SK
Panijayanond T, see Vongvises P
Pantazis KL, see Ravindran RS
Papastephanou C, see Balamoutsos NG
Papincak JF. To make the patient ready for anesthesia—medical care of the surgical patient (book review) 1984;63:1051
Paplanus SH, see Vaughan RW
Paradise RR, see Krishna G
  see Moorthy SS
  see Roesch C
Paris P. Trauma (book review) 1984;63:95
Park K, see Thiagarajah S
Park SS, see Lee KS
Park WG, see Wilson F
Park WY, Balingit PE, Macnamara TE. Effects of patient age, pH of cerebrospinal fluid, and vasopressors on onset and duration of spinal anesthesia 1975;54:455
  Epidural anesthetic spread (letter) 1981;60:227
  Hagins FM, Massengale MD, Macnamara TE. The sitting position and anesthetic spread in the epidural space 1984;63:863
  Hagins FM, Rivat EL, Macnamara TE. Age and epidural dose response (abstract) 1981;60:268
  Massengale M, Kim SI, Poon KC, Macnamara TE. Age and the spread of local anesthetic solutions in the epidural space 1980;59:768, (abstract) 1980;59:554
  Poon KC, Massengale MD, Macnamara TE. Direction of the needle bevel and epidural anesthetic spread (abstract) 1982;61:208
Parker EO, DeVore R. Central cannulation: difficulty with an errant guide wire (letter) 1982;61:394
  see Schwartz AJ
Parker FB Jr, see Gerson JI
Parker WA, see Krenzelok EP
Parkhouse J, Pleuvry BJ, Rees JMH. Analgesic drugs (book review) 1980;59:521
Parkin CE, see Hopkinson RB
Parks C, see Lundeen G
Parks RI, see Raj PP
Parmley RT, see Kim JT
Parris WCV, Gerlock AJ Jr, MacDonnell RC Jr. Intra-arterial chloroprocaine for the control of pain associated with partial splenic embolization 1981;60:112
  Quimby CW Jr. Anesthetic considerations for the patient with homocystinuria 1982;61:708
Parton ME, see Goldzimer EL
Pash MP, see Palahniuk RJ
Pashley NRT, see Lane GA
Paspa P, Tang CK, Dwarakanath R, Ramanathan S, Chalon J, Fischgrund Gk, and Turndorf H. A perculator vaporizer heated by reaction of neutralization of lime by carbon dioxide 1981,60:146
Pasque MK, see Christian CM
Patanella H, see Ona FV
Patel AK, see Azar I
Patel C, see Capan LM
  see Chalon J
  see Ramanathan S
Patel K, Bennett EJ, Grundy EM et al. Relation of $Pa_{CO_2}$ to fresh gas flow in a circle system 1976;55:706
  see Cairoli VJ
Patel KD, Dalal FY. A potential hazard of the Dräger scavenging interface system for wall suction 1979;58:327
  Gelman S. Pressor responses to naloxone and physostigmine (letter) 1980;59:517
  Henschel EO. Postoperative alopecia 1980;59:311
  Palmer SK, Phillips MF. Mainstem bronchial rupture during general anesthesia 1979;58:59
  see Tanguturi S
Patel KF, Hicks JN. Prevention of fire hazards associated with use of carbon dioxide lasers 1981;60:885
  see Wheeler AS
Patel KP, see Capan LM
  see Winnie AP
Patel TC, see Geevarghese KP
Patel YC, see Sprigge JS
  see Wynands JE
Paterson G, see McQuay H
Paterson GMC, see Cowen MJ
Pathak K, see Root B
Pathak KS, Brown RH, Cascorbi HF, Nash CL. Effects of fentanyl and morphine on intraoperative somatosensory cortical-evoked potentials 1984;63:833
  Brown RH, Nash CL Jr, Cascorbi HF. Continuous opioid infusion for scoliosis fusion surgery 1983;62:841
Patil VU, Stehling LC, Zauder HL, Chilcoat RT. An aid to blind endotracheal intubation (letter) 1984;63:882
Paton WDM, see Smith RA
Patrick RT. Regional anesthesia in children (correspondence) 1975;54:825
Patt M, see Koht A
Patten EV, see King WH
Patterson MK, see Liu PL
Patterson RW (correspondence) 1976;55:898
  Effect of $Pa_{CO_2}$ on $O_2$ consumption during cardiopulmonary bypass in man 1976;55:269
Pauca AL, Jenkins TE. Airway obstruction by breakdown of a non-rebreathing valve: how foolproof is foolproof? 1981;60:529
Paul T, see Samsi AB
Paul WL, Bishko JR, Woodham B. Succinylcholine, *d*-tubocurarine, and intracranial pressure in dogs (abstract) 1981;60:269
  Munson ES. Gas embolism during encephalography (case history) 1976;55:141
  Munson ES, Maniscalco JE. Cerebrospinal fluid pressure during $O_2$ encephalography and $N_2O$ inhalation 1976;55:849
  see Stone DR
Paulaus DA, see Kaplan RF
Paulsen AW, Kutner MH. Statistical methods, Student's *t*-test (questions and answers) 1977;56:596
  see Davis GC Jr
  see Frazier WT
Pautler S, see Albin MS
  see Newfield P

Payne JP, Bushman JA. Artifical ventilation (book review) 1981;60:541
Pearce AC, see Jones RM
Pearl RG, see Halperin BD
Pearlstein S, see Ramanathan S
Pearsall NN, see Duncan PG
Pease RD, Scanlon TS III, Herren AL, Benumof JL. Intraoperative transection of a Swan-Ganz catheter 1979;58:519
Pechnick RR, see Janowsky EC
Pedersen H, Morishima HO, Finster M, Arthur GR, Covino BG. Pharmacokinetics of etidocaine in fetal and neonatal lambs and adult sheep 1982;61:104
  see Santos A
Pelletier GB, see Boulanger M
Peltola K, see Salmenperä M
Pembleton WE. Trichloroethylene anesthesia reevaluated (correspondence) 1975;54:348
Pena R, see Galindo A
Penuelas J, see Melman E
Perel A, Eimerl D, Grossberg M. A PEEP device for a manual bag ventilator (brief reports) 1976;55:745
  Katzenelson R, Klein E, Cotev S. Collapase of endotracheal tubes to overinflation of high-compliance cuffs 1977;56:731
Perisho JA, see Crawford AH
Perkins FM, see Abajian JC
Perkins HM, see Cottrell WM
  see Stone DR
Perkins NAK, Bedford RF. Hemodynamic consequences of PEEP in seated neurological patients—implications for paradoxical air embolism 1984;63:429
Per-Lee JH, see Ghani GA
Perry JC, Munson ES, Malagodi MH et al. Venous air embolism prophylaxis with a surface-active agent 1975;54:792
Perry LB, Gould AB Jr, Leonard PF. Nonflammable fires in the operating room (case history discussion) 1975;54:152
Perry PA, see Nimocks JA
Perschau RA, Modell JH, Bright RW, Shirley PD. Suspected sodium nitroprusside-induced cyanide intoxication 1977;56:533
Persing JA, see Bedford RF
Persing JS, see Bedford RF
Perumbetti PVP, see Regan AG
Peskett WGH. Reducing the risk of acid aspiration during cesarean section (correspondence) 1975;54:520
Peters JL, see Wong KC
Peters KR, Nance P, Wingard DW. Malignant hyperthyroidism or malignant hyperthermia 1981;60:613
  see Hurlbert BJ
Peters MP, see Yagiela JA
Peters RM, see Shackford SR
  see Sise MJ
Peterson C see Stoelting RK
Peterson DD, "Shoulder block" anesthesia for shoulder reconstruction surgery (abstract) 1984;63:259
Peterson ML, see Berry AJ
Peterson RC, see Ghaneim MM
Petty C. An alternate method for internal jugular venipuncture for monitoring central venous pressure (brief reports) 1975;54:157
  Right radial artery pressure during mediastinoscopy 1979;58:428
Petty TL, Cherniack RM. Seminars in respiratory medicine (book review) 1980;59:167
Petty WC, see Blitt CD
  see Liu WS
Peuler MJ, see Burgess GE III
Pflug AE, Aasheim GM, Beck HA. Spinal anesthesia: bupivacaine versus tetracaine 1976;55:489
  Lindop MJ, Murphy TM et al. Early reversal of postoperative hypoxemia 1976;55:822
Pham NA, see Azar I
Phan CQ, see Azar I
Phelps JA, Sass DJ. A new portable battery-powered three-channel monitor (brief reports) 1975;54:546
Phero JC, see Denson DD
Phil D, see Philbin DM
Philbin DM. Anesthetic management of the patient with cardiovascular disease (book review) 1979;58:445
  Foex P, Phil D, Drummond G, Ryder WA, Jones LA. Regional ventricular function with sufentanil anesthesia: the effect of nitrous oxide (abstract) 1984;63:260
  Rosow CE, Moss J, Keegan CR, Alban J, Schneider RC. Hormonal responses with fentanyl or sufentanil: a double blind study (abstract) 1984;63:261
  see Bovill JG
  see de Lange S
  see Hill GE
  see Kono K
  see Landry LD
  see Nieminen MT
  see Sebel PS
  see Todd MM
  see Tomichek RC
  see Zaidan J
Philip BK see Philip JH
Philip JH, Philip BK. Pressurized infusion system for fluid resuscitation 1984;63:779
  see Raemer DB
Philipson EH, see Kuhnert BR
Phillips GD, Odgers CL. Parenteral & enteral nutrition (book review) 1981;60:70
Phillips KC, see Prys-Roberts C
Phillips MF, see Patel KD
Phillips OC. ASA classification (questions and answers) 1976;55:615
Phillips P, see Mogos B
Phitayakorn P, see McKenzie R
Phythyon JM, see Berman ML
Pickering BG, Bristown GK, Craig DB. Case history number 97: core rewarming by peritoneal irrigation in accidental hypothermia with cardiac arrest 1977;56:574
Pieper JA, see McNamara PJ
Pierce E, see Lees DE
Pierce J, see Gattinoni L
Pilon RN, see Lang DW
Pinaud MJL, Blanloeil YAG, Souron RJ. Preoperative prophylactic digitalization of patients with coronary heart disease—a randomized echocardiographic and hemodynamic study 1983;62:865
Pinsky MR. Advances in shock research (book review) 1983;62:1139
  Chest medicine (book review) 1983;62:959
  see Martin DJ
Pirlo AF, see Fillmore RB
Pither CE, see Ford DJ
  The Lee modification of the Tuohy needle—a useful adjunct to gauging the depth of the epidural needle (letter) 1984;63:1048
Pitt BR. Mechanisms of lung microvascular injury (Volume 384) (book review) 1983;62:462
Piziali RL, see Whitcher C
Platou ES, see Hotvedt R
Platzker ACG, see Goldberg RN
Pleet AB, see Massey EW
Pleuvry BJ, see Parkhouse J
Plotkin BS, see Ravindran RS
Plumer MH, see Berryhill RE
Plummer JL, Cousins MJ, Hall P. Hypoxia and halothane hepatoxicity (letter) 1983;62:859
Plummer MH, see Reisner LS
Pobereskin L, see Bedford RF
Pochanapring A, Moyers JR, Carter JG, Wright CB. Left stellate ganglion block for hypertension after coronary artery surgery (abstract) 1981;60:269
Pohl LR, Gillette JR. A perspective on halothane-induced hepatotoxicity 1982;61:809
Pollack S, see Root B
Pollo F, see Glisson SN
Polta TA, Hanisch EC, Nasser JG,

  Ramsborg GC, Roelofs RI. Masseter spasm after pancuronium 1980;59:509
Pond W, see Moorthy SS
Pontén J, Häggendal J, Milocco I, Waldenström A. Long-term metoprolol therapy and neuroleptanesthesia in coronary artery surgery: withdrawal versus maintenance of $\beta_1$-adrenoreceptor blockade 1983;62:380
Pontoppidan H, see Fuleihan SF
Poon KC, see Park WY
Poon YK. A life-threatening complication of cricothyroid membrane puncture (case history) 1976;55:298
Popp AJ, Bourke RS, Nelson LR, Kimelberg HK. Neural trauma (book review) 1979;58:354
Poppleton P, see Bullingham R
Porch D, see Hirshman CA
Port D, see Meuleman TR
  see Sederberg J
Port JD, see Liu WS
  see Wong KC
  Steffins J. Cardiovascular responses to asphyxial challenge in chronically hypokalemic dogs 1983;62:991
Portas MR, see Stanley TH
Porte D, see Downing JW
Porter B, see McQuay H
Ports TA, see Wilkinson PL
Posner MA, Reves JG, Lell WA. Aortic valve replacement in a hemodialysis-dependent patient: anesthetic considerations—a case report 1975;54:24
  Rodman GH, Click JM, Tobey RE. Cyanide production during nitroprusside therapy in an oliguric patient 1977;56:729
Potzick J, see Gelman S
Powell DR, Miller R. The effect of repeated doses of succinylcholine on serum potassium in patients with renal failure 1975;54:746
Prakash O, Jonson B, Meij S, Bos E, Hugenholtz PG, Nauta J, Hekman W. Criteria for early extubation after intracardiac surgery in adults 1977;56:703
Pratila MG, see Pratilas V
Pratilas V, Pratila MG, Bramis J, Smith H Jr. The hepatoprotective effect of oxygen during halothane anesthesia 1978;57:481
Prato FS, Knill RL. Diazepam sedation reduces functional residual capacity and alters the distribution of ventilation in man (abstract) 1982;61:209
Pratt JH. Gynecologic anesthesia during menses (questions and answers) 1977;56:746
Presbitero JV, Ruiz RS, Rigor BM Sr, Drouilhet JH, Reilly EL. Intraocular pressure during enflurane and neurolept anesthesia 1980;59:50
Priano LL. Alterations of renal hemodynamics by thiopental, diazepam, and ketamine in conscious dogs 1983;61:853
  Marrone B, Huber P, Arnold JA, Arens JF. An unusual catheter complication with continuous epidural anesthesia 1983;62:447
  Miller RD. Pancreatic arteriovenous malformation and celiac plexus block 1977;56:288
  see Abston PA
  Solanki D. Operating room temperature (letter) 1981;60:226
  Vatner SF. Generalized cardiovascular and regional hemodynamic effects of meperidine in conscious dogs 1981;60:649
Price JD, see Scuderi PE
Price KA, Matsumoto Y, Frederickson EL. Effect of halothane on isometric twitch and tetanus response and the associated heat production in striated muscle of frogs 1975;54:527
Prins L, see Knill R
Prior PF. Monitoring cerebral function (book review) 1980;59:84
Privitera PA, see Boyan CP
Probst S, see Latasch L
Procopio PT, see Grundy BL
Proctor JE, see Gelman S
Prough D, see Scuderi PE
Prys-Roberts C. Hypertension, ischemic heart disease and anesthesia: international anesthesiology clinics, Winter 1980, Volume 18, Number 4 (book review) 1981;60:367
  Sear JW, Low JM, Phillips KC, Dagnino J. Hemodynamic and hepatic effects of methohexital infusion during nitrous oxide anesthesia in humans 1983;62:317
  see Calverley RK
  see Cartwright P
  The circulation in anaesthesia, applied physiology and pharmacology (book review) 1980;59:895
Puchstein C, see Van Aken H
Pulver JJ, Cullen BF, Miller DR, Valenta LJ. Use of the artificial beta cell during anesthesia for surgical removal of an insulinoma 1980;59:950
Purkey I, see Kaplan RF
Purtock RV, see Turner LA
Pütsep E. Modern hospital (book review) 1980;59:317
Pyles ST, Berman LS, Modell JH. Expiratory valve dysfunction in a semiclosed circle anesthesia circuit—verification by analysis of carbon dioxide waveform 1984;63:536
  Kaplan RF, Munson ES. Gas loss from Ohio modulus vaporizer selector-interlock valve (letter) 1983;62:1052
  Scher KS, Vega ET, Harrah JD, Rubis LJ. Cannulation of the dorsal radial artery: a new technique 1982;61:876
Quan SF, see Gordon EP
  see Otto CW
  see Waterson CK
Quest DO, see Rampil IJ
Quimby CW Jr. Anesthesiology, a manual of concept and management, second edition (book review) 1980;59:85
  Law for the medical practitioner (book review) 1980;59:715
  Physician-patient relationship, legal aspects of anesthesia (questions and answers) 1976;55:463
  see Parris WCV
Quimby KL, Katz J, Bowman RE. Behavioral consequences in rats from chronic exposure to 10 ppm halothane during early development 1975;54:628
Quinby WC, see Martyn JAJ
Quinn ML, see Smith NT
Quinn P, see Garber JG
Quintin L, Whalley DG, Wynands JE, Morin JE, Mayer R. Oxygen-high dose fentanyl-droperidol anesthesia for aortocoronary bypass surgery 1981;60:412
Quiroga M, see Urzua J
Rabinovitch A, see Dauchot PJ
Rabinovitz J, see Milstein J
Rackow H, Salanitre E. The pulmonary absorption-excretion volume effect 1976;55:51
  see Salanitre E
Radding J, see Jatlow P
Radnay PA, Becsey LS, Shah NK et al. Comparison of methotrimeprazine and meperidine as components of balanced anesthesia 1975;54:749
  Duncalf D, Novakovic M, Lesser ML. Common bile duct pressure changes after fentanyl, morphine, meperidine, butorphanol, and naloxone 1984;63:441
  International anesthesiology clinics—anesthetic considerations for pediatric cardiac surgery, Volume 18, Number 1 (book review) 1980;59:813
  see Amaki Y
  see El-Gaweet EI
Radonjic R, see Winnie AP
Radtke N, Waldman J. Influence of enflurane anesthesia on intraocular pressure in youths 1975;54:212

- Raemer DB, Francis D, Philip JH, Gabel RA. Variation in $Pco_2$ between arterial blood and peak expired gas during anesthesia 1983;62:1065
- Rafferty TD, Marrero O, Nardi D, Schachter EN, Mentelos R, Hastings A, Roselli D. Relationship between transcutaneous and arterial carbon dioxide tension in adult patients anesthetized with nitrous oxide-fentanyl and nitrous oxide-enflurane 1981;60:504
  - Marrero O, Nardi D, Schacter EN, Mentelos R, Ngeow YF. Transcutaneous $Po_2$ as a trend indicator of arterial $Po_2$ in normal anesthetized adults 1982;61:252
  - Nardi D, Schachter N. Evaluation of transcutaneous $Pco_2$ monitoring in neuroanesthesia (abstract) 1981;60:270
- Ragasa JP, see Howland WS
- Rah KH, Dunwiddie WC, Lower RR. A method for continuous postoperative measurement of mixed oxygen saturation in infants and children after open heart procedures 1984;63:873
  - Griffith RL III, Jones JR, Salzberg AM. Anesthetic management of the pediatric patient with a tracheal T-tube 1981;60:445
  - see Chu SS
  - see Chu YK
  - see Shiroka A
- Raj PP, Parks RI, Watson TD et al. A new single-position supine approach to sciatic-femoral nerve block 1975;54:489
  - Rosenblatt R, Miller J, Katz RL, Carden E. Dynamics of anesthetic compounds in regional anesthesia 1977;56:110
  - see Denson DD
  - see Ford DJ
  - see Forestner JE
- Ralley FE, Ramsay JG, Wynands JE, Townsend GE, Whalley DG, DelliColli P. Effect of heated humidified gases on temperature drop after cardiopulmonary bypass 1984;63:1106
- Ralston SH, Babbs CF, Niebauer MJ. Cardiopulmonary resuscitation with interposed abdominal compression in dogs 1982;61:645
- Ramamurthy R, see Cuasay OS
- Ramamurthy S, Akkineni SR, Winnie AP. A simple technic for block of the spinal accessory nerve 1978;57:591
  - see Edwards R
  - see Winnie AP
  - Steen SN, Winnie AP. Doxapram antagonism of meperidine-induced respiratory depression 1975;54:352
- Ramanathan R, see Capan LM
- Ramanathan S, Arismendy J, Gandhi S, Chalon J, Turndorf H. Coaxial catheter for humidification during jet ventilation 1982;61:689
  - Capan L, Chalon J, Pearlstein S, Turndorf H. Cardiac output estimation by $CO_2$ rebreathing method in dogs anesthetized on the Bain anesthesia circuit (abstract) 1980;59:555
  - Chalon J, Capan L, Patel C, Turndorf H. Rebreathing characteristics of the Bain anesthesia circuit 1977;56:822
  - Chalon J, Patel C. Rebreathing characteristics of Bain anesthesia circuit (correspondence) 1978;57:376
  - Chalon J, Rand P et al. Humidity output of the Columbia pediatric circle (brief reports) 1976;55:877
  - Chalon J, Richards M, Patel C, Turndorf H. Prolonged spinal nerve involvement after epidural anesthesia with etidocaine 1978;57:361
  - Chalon J, Satyanarayana T, Arismendy J, Turndorf H. Continuous and simultaneous on-line measurements of $\dot{V}o_2$ and $\dot{V}co_2$ during endotracheal anesthesia 1982;61:362
  - Chalon J. Thermometric estimation of carbon dioxide output in the anesthetized patient 1975;54:206
  - Chalon J, Turndorf H. A safety valve for the pediatric Rees system (brief reports) 1976;55:741
  - Friedman S, Moss P, Arismendy J, Turndorf H. Phenylephrine for the treatment of maternal hypotension due to epidural anesthesia (abstract) 1984;63:262
  - Gandhi S, Arismendy J, Chalon J, Turndorf H. Oxygen transfer from mother to fetus during cesarean section under epidural anesthesia 1982;61:576
  - Gandhi S, Arismendy J, Chalon J, Turndorf H. Relationship between $FaO_2$ and fetal oxygenation during cesarean section under epidural anesthesia (abstract) 1982;61:210
  - Gupta U, Chalon J, Turndorf H. Anesthetic considerations in Takayasu arteritis 1979;58:247
  - Masih AK, Ashok U, Arismendy J, Turndorf H. Concentrations of lactate and pyruvate in maternal and neonatal blood with different intravenous fluids used for prehydration before epidural anesthesia 1984;63:69
  - Masih AK, Rock I, Chalon J, Turndorf H. Maternal and fetal effects of prophylactic hydration with crystalloids or colloids before epidural anesthesia 1983;62:673
  - see Amirdivani M
  - see Buffington DW
  - see Capan LM
  - see Chalon J
  - see Paspa P
  - see Satyanarayana TV
  - see Sivakumaran C
  - see Tang CK
- Ramirez-Inawat RC, see Kopman EA
  - see Krechel SLW
- Rampil IJ, Holzer JA, Quest DO, Rosenbaum SH, Correll JW. Prognostic value of computerized EEG analysis during carotid endarterectomy 1983;62:186
- Ramsay JG, see Ralley FE
- Ramsborg GC, see Polta TA
- Ramsey FM, Lebowitz PW, Savarese JJ, Ali HH, deBros FP. Neuromuscular and hemodynamic effects of pancuronium-metocurine combination (abstract) 1981;60:271
  - Lebowitz PW, Savarese JJ, Ali HH. Succinylcholine neuromuscular block reexamined (letter) 1980;59:633
  - see Lebowitz PW
  - see Weeks DB
  - Lebowitz PW, Savarese JJ, Ali HH. Clinical characteristics of long-term succinylcholine neuromuscular blockade during balanced anesthesia 1980;59:110
- Ramzan IM, Shanks CA, Triggs EJ. Gallamine cumulation ratios (letter) 1981;60:912
  - Shanks CA, Triggs EJ. Pharmacokinetics and pharmacodynamics of gallamine triethiodide in patients with total biliary obstruction 1981;60:289
- Rand P, see Ramanathan S
- Rao CC, Krishna G, Grosfeld JL, Weber TR. One-lung pediatric anesthesia 1981;60:450
  - Krishna G, Trueblood S. Stenting of the endotracheal tube to manage airway obstruction in the prone position 1980;59:700
  - see Dierdorf SF
  - see Haselby KA
  - see Roesch C
- Rao DBS, see Matsuo S
- Rao LN, see Grundy EM
- Rao M, see Weinberg S
- Rao TLK, Colloid or crystalloid? (letter) 1981;60:228
  - El-Etr AA. Fentanyl and convulsions (letter) 1983;62:859
  - El-Etr AA. Myocardial reinfarction

following anesthesia in patients with recent infarction (abstract) 1981;60:271
  El-Etr AA. Right ventricular function in pulmonary hypertension—role of nitroglycerin (abstract) 1984;63:263
  Jacobs HK. Pulmonary function following 'pretreatment' dose of pancuronium in volunteers 1980;59:659
  Jacobs HK, Salem MR, Santos P. Deliberate hypotension and anesthetic requirements of halothane 1981;60:513
  Madhavareddy S, Chinthagada M, El-Etr AA. Metoclopramide and cimetidine to reduce gastric fluid pH and volume 1984;63:1014
  Mummaneni N, El-Etr AA. Convulsions: an unusual response to intravenous fentanyl administration 1982;61:1020
  see Gorski DW
  see Mathru M
  see Mummaneni N
  Shanmugham M. Succinylcholine administration—another contraindication? 1979;58:61
  Suseela M, El-Etr AA. Metoclopramide and cimetidine to reduce gastric juice pH volume (abstract) 1984;63:264
Rapp RP, see Dorris GG
Rappolt RT Sr, see Gay GR
Rarey KP, Youtsey JW. Respiratory patient care (book review) 1981;60:T22
Rattenborg CC, Via-Reque E. Clinical uses of mechanical ventilation (book review) 1982;61:959
Rau JL Jr. Respiratory therapy pharmacology (book review) 1979;58:67
Ravin MB. How do benefits of hemodilution balance $O_2$ reduction? (correspondence) 1976;55:898
  Newmark Z, Saviello G. Myotonia dystrophica—an anesthetic hazard: two case reports 1975;54:216
  Problems in anesthesia: A case study approach (book review) 1982;61:311
  Pyridostigmine as an antagonist of *d*-tubocurarine-induced and pancuronium-induced blockade 1975;54:317
  see Dorris GG
  see Gordon RJ
Ravindran RS. A simple technique to stop hiccups during endotracheal anesthesia (letter) 1981;60:121
  Albrecht WH, McKay M. Apparent intravascular migration of epidural catheter 1979;58:252
  Albrecht WH. Precordial chest pain during spinal or epidural anesthesia (letter) 1983;62:1134
  Albrecht WH, Tasch M. Low pressure headache following successful continuous lumbar epidural analgesia 1980;59:799
  Baldwin SJ. Percutaneous spinal catheterization in dogs: a new technique (letter) 1981;60:618
  Bates ML, Strausburg BJ, Chambers WA, Littlewood DG, Logan MR, Scott DB. Epinephrine and duration of spinal anesthesia (letter) 1982;61:395
  Bond VK, Tasch MD, Gupta CD, Luerssen TG. Prolonged neural blockade following regional analgesia with 2-chloroprocaine 1980;59:447
  Cummins DF, Pantazis KL, Strausburg BJ. Baenziger JC. Measurement of pseudocholinesterase (letter) 1983;62:618
  Cummins DF, Pantazis KL, Strausburg BJ, Baenziger JC. Unusual aspects of low levels of pseudo-cholinesterase in a pregnant patient 1982;61:953
  Cummins DF, Smith IE. Experience with the use of nitroprusside and subsequent epidural analgesia in a pregnant quadriplegic patient 1981;60:61
  Dryden GE, Somerville GM. Treatment of priapism with ketamine and physostigmine 1982;61:705
  Epidural autologous blood patch on an outpatient basis (letter) 1984;63:962
  Gupta CD, Stoops CA. Epidural analgesia in the presence of herpes simplex virus (type 2) infection (letter) 1982;61:714
  Klemm JE. Allergy to succinylcholine (letter) 1981;60:456
  Klemm JE. Anaphylaxis to succinylcholine in a patient allergic to penicillin 1980;59:944
  Plotkin BS. Simple technique to replace a central venous catheter with a pulmonary arterial catheter (letter) 1981;60:229
  see Viegas OJ
  Stoops CM. Anesthetic management of a patient with Hallermann-Streiff syndrome 1979;58:254
  Tasch MD, Baldwin SJ, Hendrie M. Subarachnoid injection of autologous blood in dogs is unassociated with neurologic deficits 1981;60:603
  Turner MS, Muller J. Neurologic effects of subarachnoid administration of 2-chloroprocaine-CE, bupivacaine, and low pH normal saline in dogs 1982;61:279
  Viegas OJ, Padilla LM, LaBlonde P. Anesthetic considerations in pregnant patients receiving terbutaline therapy 1980;59:391
  Viegas OJ, Tasch MD, Cline PJ, Deaton RL, Brown TR. Bearing down at the time of delivery and the incidence of spinal headache in parturients 1981;60:524
  Viegas OJ. Transient lower extremity weakness in an obstetric patient unrelated to epidural anesthesia 1981;60:527
Rawal N, Möllerfors K, Axelsson K, Lingårdh G, Widman B. An experimental study of urodynamic effects of epidural morphine and of naloxone reversal 1983;62:641
  Sjöstrand U, Christoffersson E, Dahlström B, Arvill A, Rydman H. Comparison of intramuscular and epidural morphine for postoperative analgesia in the grossly obese: influence on postoperative ambulation and pulmonary function 1984;63:583
  Sjöstrand U, Dahlström B. Postoperative pain relief by epidural morphine 1981;60:726
  Sjöstrand UH, Dahlström B, Nydahl PA, Östelius J. Epidural morphine for postoperative pain relief: a comparative study with intramuscular narcotic and intercostal nerve block 1982;61:93
  Wattwil M. Respiratory depression after epidural morphine—an experimental and clinical study 1984;63:08
Rawitscher RE, see Gordon RJ
Rawson JE, see Lough MD
Raya J, see Abboud T
Rayburn RL, see Ausinsch B
  Watson RL. Humidity in children and adults using CPRAM (abstract) 1980;59:556
Raymon F, see Funk D
Raymond MJ, see Moffitt EA
  see Sethna DH
Read WA, see Fibuch EE
Ready LB. An aid to rapid intravenous infusion 1979;58:155
  see Bashein G
Ream AK, see Gravenstein JS
Redderson CL, see Anton AH
Reddy P, see Sederberg J
Reddy RV, see Moorthy SS
Reder BS, Trapp LD, Troutman KC. Ketamine suppression of chemically induced convulsions in the two-day-old white Leghorn cockerel 1980;59:406
Redford JE, see Gorsky BH

Reed JP. Transtracheal ventilation (letter) 1983;62:457

Reed S, see Rosenberg H

Reekers-Ketting JJ, see Vree TB

Rees DI, Gaines GY III. One-lung anesthesia—a comparison of pulmonary gas exchange during anesthesia with ketamine or enflurane 1984;63:521

- Wansbrough SR. One-lung anesthesia: percent shunt and arterial oxygen tension during continuous insufflation of oxygen to the nonventilated lung 1982;61:507

Rees JMH, see Parkhouse J

Reese ALP, see Kuhnert BR

Refsum H, see Hotvedt R

Regan AG, Perumbetti PVP. Pancuronium and gentamicin interaction in patients with renal failure (letter) 1980;59:393

Regan BM, see Wallin RF

Rege A, see Subaiya L

Rehder K, see Beynen FM

Rehn J. Der alte Mensch in der Chiturgie (book review) 1980;59:227

Reich JG, see Rosenblatt RM

- see Stewart MS

Reichert TJ, see Johans TG

Reilley TE, see Howie MB

Reilly EL, see Presbitero JV

Reimer DH. A life-threatening complication of cricothyroid membrane puncture (case history) 1976;55:299

Reisner LB. Bicitra is 0.3 molar sodium citrate (letter) 1982;61:801

Reisner LS, Hochman BN, Plumer MH. Persistent neurologic deficit and adhesive arachnoiditis following intrathecal 2-chloroprocaine injection 1980;59:452

- Lippmann M. Further data on epinephrine interactions (correspondence) 1977;56:468
- Lippmann M. Ventricular arrhythmias after epinephrine injection in enflurane and in halothane anesthesia 1975;54:468
- see Ward CF

Reitan JA. Effect of halothane on systolic time intervals (guest discussion) 1977;56:524

- James OF, Martucci RW. Cardiovascular effects of atropine sulfate preparations in vagotomized dogs under halothane anesthesia 1977;56:338
- Lim A. Automated measurement and frequency analysis of the pneumocardiogram 1978;57:647
- see Safwat AM
- Stengert KB, Wymore ML, Martucci RW. Central vagal control of fentanyl-induced bradycardia during halothane anesthesia 1978;57:31
- Warpinski MA, Martucci RW. Determinants and genesis of canine pneumocardiogram 1978;57:653

Reitz BA, see Mihm FG

Reitz J, MacKichan JJ, Hoffer L, Kryc J, Howie MB. Reduced plasma clearance of alfentanil associated with prolonged major intra-abdominal surgery (abstract) 1984;63:265

Reiz S, see Bålfors E

Remine WH. Gynecologic anesthesia during menses (questions and answers) 1977;56:746

Renck R, see Aldrete JA

Rendell-Baker L. Bottle adaptors for vaporizers (letter) 1979;58:156

- Meyer A. Ventilator low pressure alarm works well if wider bore gas supply tubing is used (letter) 1984;63:883
- Milliken RA, Garro A. Halothane mutagenicity (letter) 1979;58:64
- Purity of oxygen, USP (letter) 1980;59:314
- Reinforced tracheal tube hazard alert (letter) 1980;59:519
- see Mushin WW
- Some gas machine hazards and their elimination 1976;55:26
- Sterilization of ampules by ethylene oxide (questions and answers) 1977;56:743

Rendon-Platas AM, see Toro-Matos A

Reneman RS, see van der Vusse GJ

- see van der Starre PJA

Restall CJ. Plastic-covered wire stylet (correspondence) 1976;55:755

- Schmidt SP. A warmer for antiseptic skin preparation solutions 1977;56:124

Reves JG, Karp RB, Oparil S, Samuelson PN, Tosone S, Smith LR. Cathecholamine changes during cardiopulmonary bypass: the stress response and role of the lungs in modulating it (abstract) 1981;60:272

- Kissin I, Fournier SE, Smith LR. Additive negative inotropic effect of a combination of diazepam and fentanyl 1984;63:97
- McCracken LW Jr. Failure to induce hepatic pathology in animals sensitized to a halothane metabolite and subsequently challenged with halothane 1976;55:235
- see Eini M
- see Dundee JW
- see Gelman S
- see Kissin I
- see Laflin MJ
- see Motomura S
- see Naulty JS
- see Posner MA
- see Samuelson PN
- see Shepard LS
- see Tosone SR
- see Vinik HR
- Spain JA, Alvis JM, Ritchie RG. Continuous infusion of fentanyl during cardiac anesthesia: an automated system (abstract) 1984;63:266
- Steroids and anesthesia (correspondence) 1978;57:379

Reyes-Guerra A. Modern anesthesia in dentistry (book review) 1980;59:227

Reynolds AC, see Abram SE

Reynolds AF, Hameroff SR, Blitt CD, Roberts WL. Spinal subdural epiarachnoid hematoma, a complication of a novel epidural blood patch technique 1980;59:702

- see Dautenhahn D

Reynolds ES. Trichloroethylene anesthesia re-evaluated (correspondence) 1975;54:348

Reynolds F. Epidural narcotics (letter) 1981;60:123

- Neonatal neurobehavioral responses (letter) 1984;63:1045

Rhee CW, see Smith DJ

Rice SA, see Baden JM

- see Mazze RI

Richards JR, Kinney JM. Nutritional aspects of care in the critically ill (book review) 1980;59:317

Richards M, see Ramanathan S

Richards SD. A method for securing pediatric endotracheal tubes 1981;60:224

Richey ET, see Gallagher TJ

Ricker SM, see Stirt JA

Ridgley E, see Saleh SA

Rieser JC. Pre-and-post anesthetic use of atropine in patients with glaucoma (questions and answers) 1976;55:460

Riess W, see Lanz E

Riggi SJ, Moore DC. Chloroprocaine: neurotoxicity and formulations in perspective (letter) 1982;61:715

Rigor BM, see Presbitero JV

Rigor BM Sr, see Hunt JR

Rimerman V, see Gelman S

Rinaldo J. Update: pulmonary diseases and disorders (book review) 1984;63:171

Ring WH, Adair JC, Elwyn RA. New pediatric endotracheal tube (brief reports) 1975;54:273

- see Adair JC
- see Elwyn RA

Riordan KK, see Weiskopf RB

Ritchie RG, see Reves JG

Ritter JG, Anderson N. Comparison of

dot test and digit-symbol test for street fitness of outpatients 1976;55:883
Ritter JW, Shigezawa GY
Roe SD Sr, Sullivan SF. Increasing myocardial oxygen demand during prolonged halothane anesthesia in dogs 1983;62:788
Ritzman JR, Erickson HH, Miller ED. Cardiovascular effects of enflurane and halothane on the Rhesus monkey 1976;55:85
Rivat EL, see Park WY
Rizk SF, see Berry AJ
Rizor RF, see Lynch C III
Roaf ER, see Desai SP
Roberson VO, see Brown DR
Roberts JT, see Fahmy NR
Roberts KW. New use for Swan-Ganz introducer wire (letter) 1981;60:67
Roberts RB. Antacids and glycopyrrolate (correspondence) 1978;57:145
Blind esophageal intubation to divert gastric contents (correspondence) 1977;56:598
Pulmonary aspiration (book review) 1977;56:759
Reducing the risk of acid aspiration during cesarean section (correspondence) 1975;54:520
see Tausk HC
Shirley MA. Reducing the risk of acid aspiration during cesarean section (correspondence) 1975;54:241
Roberts TH, see Wong KC
Roberts TS, see Wong KC
Roberts WL, see Reynolds AF
Robertson DM, see Backer CL
Robin ED. Extrapulmonary manifestations of respiratory disease (book review) 1979;58:67
Robinson J, see Kim JM
see Loeser EA
Robinson JD, see Ido Y
Robinson MS, see Hameroff SR
Robinson S, Gregory GA. Fentanyl–air–oxygen anesthesia for ligation of patent ductus arteriosus in preterm infants 1981;60:331
Gregory GA. Fentanyl–air/$O_2$ anesthesia for PDA ligation in infants less than 1500 g (abstract) 1980;59:556
see Cahalan MK
see Cameron CB
Robotham JL, see Hoff BH
Robson JA, Brodsky JB. Latent dural puncture after lumbar epidural block 1977;56:725
Rocco AG, Francis DM, Wark JA, Concepcion MA, Covino BG. A clinical double-blind study of dibucaine and tetracaine in spinal anesthesia 1982;61:133
Mallampati R, Boon J, Concepcion MA, Covino BG. A double-blind evaluation of intrathecal bupivacaine and tetracaine (abstract) 1984;63:267
see Concepcion M
see Sheskey MC
Rock I, see Ramanathan S
Rockoff MA, see Dunlop BJ
see Levy JH
see Marsh ML
Rodman GH, see Posner MA
Rodriguez R, Gold MI. Enflurane as a primary anesthetic agent for patients with chronic obstructive pulmonary disease 1976;55:806
see Moffitt EA
Roe CR, see Lell WA
Roe SD Sr, see Ritter JW
see Stirt JA
Roelofs RI, see Polta TA
Roemer MI. Ambulatory health services in America: past, present and future (book review) 1982;61:398
Roerig DL, see Kotrly KJ
Roesch C, Haselby KA, Paradise RR, Krishna G, Dierdorf S, Wolfe TM, Rao CC. Comparison of cardiovascular effects of thiopental and pentobarbital at equivalent levels of CNS depression 1983;62:749
Rogers D, see Lawson NW
Rogers K, Chelly J, Merin RG, Taylor A. Verapamil–halothane interaction in the chronically instrumented dog (abstract) 1984;63:268
Rogers MC, see Baskoff JD
see Donegan J
Weisfeldt ML, Traystman RJ. Cerebral flood flow during cardiopulmonary resuscitation 1981;60:73
Rogge P, see Eisele JH
Rohner RF, see Dobkin AB
Roizen MF. But what does it do to outcome? (editorial) 1984;63:789
Hamilton WK, Sohn YJ. Treatment of increased PCWP by increasing the dose of enflurane or halothane (abstract) 1981;60:273
see Cahalan MK
see Harper MH
see Joyce JT
see Moss J
Sohn YJ, L'Hommedieu CS, Wylie EJ, Ota MK. Operating room temperature prior to surgical draping, effect on patient temperature in recovery room 1980;59:852, (abstract) 1980;59:557
Sohn YJ, Wylie EJ, Ota MK. Operating room temperature (letter) 1981;60:227
Stevens WC. Arrhythmogenicity of theophylline and halothane used in combination (letter) 1979;58:259
Stevens WC. Multiform ventricular tachycardia due to the interaction of aminophylline and halothane 1978;57:738
Turkey K, Ebert PA, Frazer BA. Blood flow, not low $O_2$ or pH, causes catechol response to shock in lambs (abstract) 1982;61:210
Rokowski WJ, Gurmarnik S. Laryngoscope blades modified for neonates and infants (letter) 1983;62:241
Roland CG. Terminology in anesthesia (questions and answers) 1975;54:640
Thoughts about medical writing:
XXIX. Authorship—who, and where? 1975;54:366
XXVII. Adam's rib and the anatomy of medical prose 1975;54:139
XXVIII. What hue are you? 1975;54:230
XXX. Crooked thinking 1975;54:540
XXXI. The letter to the editor 1975;54:626
XXXII. So you want to publish a book 1975;54:814
XXXIII. Parallelism is a virtue 1976;55:139
XXXIV. The publication process 1976;55:261
XXXV. "Let's call it hebetization" 1976;55:366
XXXVI. Writing an editorial 1976;55:534
XXXVII. Verify your references 1976;55:717
Rolbin SH, Levinson G, Shnider SM, Wright RG. Anesthetic considerations for myasthenia gravis and pregnancy 1978;57:441
see Abboud TK
Rolfe M, see Bullingham R
Rollason WN. Electrocardiography for the anaesthetist (book review) 1980;59:637
Romagnoli A, see Koska AJ III
Romano E. Hemodynamic monitoring with pocket calculators (letter) 1981;60:67
Romo-Salas F, see Aldrete JA
see Arguelles JE
see Cullen JP
Ronai AK, see Berry AJ
Ronfeld RA, see de Jong RH
see Knight PR
Rooke NT, Milne B. Acute pulmonary edema after regional anesthesia with lidocaine and epinephrine in a patient with chronic renal failure 1984;63:363
Rooney SM, Jain S, Goldiner PL. Effect of transcutaneous nerve stimulation on postoperative pain after thoracotomy 1983;62:1010

Rooney SM—*continued*
  see Goldiner PL
  see Vuckovic DD
Root B, Levy MN, Pollack S, Lubert M, Pathak K. Gas embolism death after laparoscopy delayed by "trapping" in portal circulation 1978;57:232
Rorie DK, Byer DE, Nelson DO, Sittipong R, Johnson KA. Assessment of block of the sciatic nerve in the popliteal fossa 1980;59:371
  Muldoon SM. Effects of fentanyl on adrenergic function in canine coronary arteries 1981;60:21
  see Ward EM
  Tyce GM, Mackenzie RA. Evidence that halothane inhibits norepinephrine release from sympathetic nerve endings in dog saphenous vein by stimulation of presynaptic inhibitory muscarinic receptors 1984;63:1059
  Vocal cord paresis following endotracheal intubation (questions and answers) 1977;56:322
Rose DK, Froese AB. Changes in respiratory pattern affect dead space/tidal volume ratio during spontaneous but not during controlled ventilation, a study in pediatric patients 1980;59:341
Rose DM, see Bassell GM
Rose JC, see Kim YD
Roselli D, see Rafferty TD
Rosen M, Latto IP, Shang W. Handbook of percutaneous central venous catheterization (book review) 1982;61:398
Rosen MA, Baysinger CL, Shnider SM, Dailey PA, Norton M, Curtis JD, Collins M, Davis RL. Evaluation of neurotoxicity after subarachnoid injection of large volumes of local anesthetic solutions 1983;62:802
  Chloroprocaine not absolved of neurotoxicity (letter) 1984;63:545
  Hughes SC, Shinder SM, Abboud TK, Norton M, Dailey PA, Curtis JD. Epidural morphine for the relief of postoperative pain after cesarean delivery 1983;62:666
  see Hughes SC
Rosen MG, see Kuhnert BR
Rosenbaum SH, Askanazi J, Hyman AI, Kinney JM. Breathing patterns during curare-induced muscle weakness 1983;62:809
  see Rampil IJ
Rosenberg H. Anesthesia orientation for the medical student 1975;54:328
  Kiykhak MM. Distance to the epidural space in nonobstetric patients (letter) 1984;63:539
  Malignant hyperthermia syndrome (correspondence) 1977;56:466
  Orkin FK, Springstead J. Abuse of nitrous oxide 1979;58:104
  Reed S. In vitro contracture tests for susceptibility to malignant hyperthermia 1983;62:415
  see Doll DC
  see Martin DE
Rosenberg MB, Levesque PR, Bourke DL. Use of the LTA kit as a guide for endotracheal intubation 1977;56:287
  Solod E, Bourke DL. Gas leak through a Fluotec Mark III vaporizer 1979;58:239
Rosenberg PH, Oikkonen MP, Orko RH, Scheinin BMA. A transplanted liver rapidly begins to metabolize enflurane in humans 1984;63:1131
  see Kalso EA
Rosenblatt R, Dennis P, Draper LD. A new method for massive fluid resuscitation in the trauma patient 1983;62:613
  see Raj PP
Rosenblatt RM. Continuous femoral anesthesia for lower extremity surgery 1980;59:631
  Domb CH. Herpangina in an anesthesiologist 1980;59:384
  Hetherington A. Failure of transcutaneous electrical stimulation to alleviate experimental tourniquet pain 1981;60:720
  Reich J, Dehring D. Tricyclic antidepressants in treatment of depression and chronic pain: analysis of the supporting evidence 1984;63:1025
  see Stewart MS
  Weaver JM, Wang Y, Tallman RD Jr. Verapamil potentiates the toxicity of local anesthetics (abstract) 1984;63:269
Rosenfeld L, see Cook DR
Rosenthal DA, see Burkett L
Rosenthal J, see Ball CG
Rosenthal JT, see Freilich JD
Rosenthal MH, see Halperin BD
Roskamm H, Schmuziger M. Coronary heart surgery (book review) 1980;59:318
Rosko TJ, Stirt JA, Sullivan SF. Aminophylline (letter) 1982;61:307
Rosner MJ, see Schettini A
Rosow CE, Keegan CR. Butorphanol vs. morphine: dose-related suppression of the response to intubation (abstract) 1984;63:270
  see Kono K
  see Nieminen MT
  see Philbin DM
  see Tomicheck RC
Ross K, see Kopman AF
Ross WT Jr, Daggy BP. Hepatic blood flow in phenobarbital treated rats during halothane and hypoxia (abstract) 1980;59:558 1981;60:306
  Hepatic blood flow, halothane, and hypoxia (letter) 1981;60:769
Rosso P, Bassi JA. Ketamine–pentobarbital maternal anesthesia and fetal survival in the guinea pig (correspondence) 1977;56:472
Rothblatt A, see Chalon J
Rothschild JM. Synopsis of critical care (book review) 1984;63:787
Rothstein P, Lister G. Epiglottitis—duration of intubation and fever 1983;62:785
  Lister G. Epiglottitis: clinical course and criteria for extubation (abstract) 1982;61:211
  Lister G. Extubation in epiglottitis (letter) 1984;63:470
Rouby JJ, Gory G, Gavaeu T, Glaser P, Viars P. Dangerous rise in pulmonary wedge pressure following aortography in a patient with a pheochromocytoma 1980;59:154
  see Benhamou D
Rouman WC, see Kay J
Rouse JM, see Bevan DR
Roush JR, see Manchikanti L
Rowland RG, see Moorthy SS
Rowlingson JC, Moscicki JC, DiFazio CA. Anesthetic potency of dezocine and its interaction with morphine in rats 1983;62:899
  see Delaney TJ
  see Friedman GA
  see Simon DL
Roxas RS, see Marquez X
Roy RC. Rational use of reversal agents (letter) 1981;60:120
Roy WL, see Blaise G
Rubbo TJ, Gergis SD, Sokoll MD. Comparative neuromuscular effects of lincomycin and clindamycin 1977;56:329
Rubin AS, Brown JL, Wortham BG, Baysinger CL. Inability to inject local anesthetic into the subarachnoid space (letter) 1984;63:783
Rubis LJ, see Pyles ST
Rucquoi M, see Camu F
Rudd GD, see Brandom BW
Rudehill A, Lagerkranser M, Lindquist C, Gordon E. Effects of mannitol on blood volume and central hemodynamics in patients undergoing cerebral aneurysm surgery 1983;62:875
Rudolph J, see Mayhew JF

Ruiz B, see Lanz E
Ruiz BC, see James CF
Ruiz RS, see Presbitero JV
Rusch JR, see Vucins EJ
Rushin JM, see Smith DJ
Rusin WD, see Walts LF
Russo P, see Meltzer HY
Rusy BF, see Ewart RBL
  see Komai H
  see Neilsen NC
Rutherford R, see Aldrete JA
Ruzbarsky J, see Suzukawa M
Ryan DW. Lymph leakage following catheterization of the right subclavian vein 1978;57:123
  see Hughes DG
Ryan WP, see Cestone KJ
Ryder WA, see Coetzee A
  see Philbin DM
Rydman H, see Rawal N
Rydvall A, see Bålfors E
Saab M, see Baraka A
Sabawala PB, see Koska AJ III
Sachatello CR, see Tsueda K
Sada T, see Nicholson JA
Sadagopan S, see El-Naggar
Sadeghi AM, see Mihm FG
Sadove MS. Hepatitis after use of two different fluorinated anesthetic agents (correspondence) 1975;54:125
Sadri S, see Abboud T
Safar P. Advances in cardiopulmonary resuscitation (book review) 1978;57:290
  see Frey R
  see Grenvik A
Safwat AM, Reitan JA, Misle GR, Hurley EJ. Use of propranolol to control rate-pressure product during cardiac anesthesia 1981;60:732, (abstract) 1981;60:274
Sage DJ, Feldman HS, Arthur GR, Datta S, Ferretti AM, Norway SB, Covino BG. Influence of lidocaine and bupivacaine on isolated guinea pig atria in the presence of acidosis and hypoxia 1984;63:01
Sahlestdt B, see Modig J
Saidman LJ, see Arkin DB
  see Berryhill RE
  see Diamant M
  Smith NT. Monitoring in anesthesia (book review) 1978;57:601
Saito H, see Akutagawa T
Saka DM, Marx GF. Management of a parturient with cardiac valve prosthesis 1976;55:214
Sakabe T, see Kuramoto T
Sakamoto K, see Yasubara H
Saksena R, see Kalia PK
Salanitre E, Rackow H. $N_2O$ volumes absorbed and excreted during $N_2O$ anesthesia in children 1976;55:95
  see Matteo RS
  see Rackow H
Saleem A, see Saleh-Shenaq S
Saleh SA, Crawford ES, Bomberger RA, Ridgley E, Morrow DH. Intraoperative acid-base management for the resection of thoracoabdominal aortic aneurysms: a comparison of continuous infusion of sodium bicarbonate versus the bolus (abstract) 1982;61:213
Saleh-Shenaq S, Saleem A, Yawn D, Harsberger K, Diemunsch P, Mohindra P. Heparin monitoring during cardiopulmonary bypass (CPB) (abstract) 1984;63:271
Salem MR. Amitriptyline therapy increases electrocardiographic changes during reversal of neuromuscular blockade (guest discussion) 1978;57:81
  see Baraka A
  see Cuasay OS
  see Heyman HJ
  see Rao TLK
Salhab AS, Nooh NG, Dujovne CA. Hepatocyte responses to volatile anesthetics: changes in surface scanning and enzyme leakage 1978;57:605
Salmenperä M, Peltola K, Takkunen O, Heinonen J. Cardiovascular effects of pancuronium and vecuronium during high-dose fentanyl anesthesia 1983;62:1059
  see Erkola O
Salts L, Ott M, Walson PD. Local anesthetic agents—pharmacologic basis for use in obstetrics (review) 1976;55:829
Saltzman LS, Kates RA, Corke BC, Norfleet EA, Heath KR. Hyperkalemia and cardiovascular collapse after dantrolene and verapamil administration in swine (abstract) 1984;63:272, 1984;63:473
Saluja TS, see Snow JC
Salvatierra O Jr, see Cronnelly R
Salvatore A, see Lee JH
Salzberg AM, see Rah KH
Samaja M, see Gattinoni L
Samoy VS, see Hameroff SR
Sampliner JE, see Berk JL
Sampson JF, Hamstra R, Aldrete JA. Management of hemophiliac patients undergoing surgical procedures 1979;58:133
Samra SK. Endotracheal tube in place passing through bite block (letter) 1981;60:66
  Migration of physicians to and from anesthesiology (letter) 1983;62:124
  see Pandit UA
Samsi AB, Bhalerao RA, Shah SC, Mody BB, Paul T, Satoskar RS. Evaluation of centbucridine as a local anesthetic 1983;62:109
Samuels SI, Clark RW. Profound atelectasis during anesthesia 1980;59:792
  Maze A, Albright G. Cardiac arrest during cesarean section in a chronic amphetamine abuser 1979;58:528
  see Merrill DG
  Washington E. Coma and abnormal neurologic signs following premedication 1980;59:79
Samuelson PN, Reves JG, Koucboukos NT, Smith LR, Dole KM. Hemodynamic responses to anesthetic induction with midazolam or diazepam in patients with ischemic heart disease 1981;60:802
  see Bini M
  see Dundee JW
  see Reves JG
Samuelson RJ, Giesecke AH Jr, Kallus FT et al. Lincomycin-curare interaction 1975;54:103
San Juan AC Jr, Stanley TH. Pulmonary embolism after tourniquet inflation (letter) 1984;63:374
Sanchala V, see Kubal K
Sanchez MM, see Glisson SN
Sanders DB, see Stilz RJ
Sanders JH, Gardner LB. Handbook of medical emergencies, second edition (book review) 1980;59:228
  see Wilkinson CJ
Sandison JW. Missionary anesthesia (correspondence) 1975;54:819
Sanfelippo PM, see Downs JG
Sanford TJ, see Shapiro HM
  see Smith NT
Santavirta S, see Kalso EA
Santora AH, see Ingram CT
Santos A, Datta S. Prophylactic use of droperidol for control of nausea and vomiting during spinal anesthesia for cesarean section 1984;63:85
  Pedersen H, Finster M, Edström H. Hyperbaric bupivacaine for spinal anesthesia in cesarean section 1984;63:1009
Santos ML, see Gonzalez-Miranda F
Santos P, see Rao TLK
Sanzone CF, see Shah NK
Saraiva RA, see Couto da Silva JMC
Sari A, Okuda Y, Takeshita H et al. Factors affecting $A\text{-}aDo_2$ after open-heart surgery 1976;55:315
Sarkis F, see Abboud TK
Sarnaik AP, see Vernon DD
Sarnquist FH, Demas K. The silent ventilator (letter) 1982;61:713
Sarwar H, Sprague DH. Laryngospasm as

Sarwar H—*continued*
  an early indicator of aspiration 1978;57:119
Sass DJ, see Phelps JA
Satinover I, see Hoffman WE
Sato S, see Dubois MY
Satoskar RS, see Samsi AB
Satou M, see Hashimoto Y
Satyanarayana TV, Capan LM, Ramanathan S. Bronchofiberscopic jet ventilation (letter) 1981;60:68
Satyanarayana TV, Capan LM, Ramanathan S, Chalon J, Turndorf H. Bronchofiberscopic jet ventilation 1980;59:350
  see Capan LM
  see Ramanathan S
  see Sivakumaran C
Saucier N, Walts LF, Moreland JR. Patient awareness during nitrous oxide, oxygen and halothane anesthesia 1983;62:239
Savarese J. Succinylcholine, avoidance of side effects (questions and answers) 1975;54:637
Savarese JJ, Antonio RP, Ginsburg S. Potential clinical uses of short-acting nondepolarizing neuromuscular-blocking agents as predicted from animal experiments 1975;54:669
  Effect of neostigmine on intestine (questions and answers) 1977;56:594
  How many neuromuscular blocking drugs affect the state of general anesthesia? (editorial) 1979;58:449
  Pharmacology of neuromuscular function (book review) 1983;62:463
  see Ali HH
  see Basta SJ
  see Donlon JV Jr
  see Lebowitz PW
  see Martyn JAJ
  see Ramsey FM
  see Zaidan J
Saviello GM. Cardiac decompensation during enflurane anesthesia in a patient with myotonia atrophica (case history comment) 1976;55:435
  see Ravin MB
Sawa T, see Colgan FJ
Sawhney KK, North AF. Anesthesia circuit tube support strap (letter) 1982;61:160
Sawyer DC, Ely SW, Korthuis RJ, Scott JB. Effects of halothane on right coronary circulation in the dog (abstract) 1980;59:559
  Hartsfield SM, Howard DR et al. Comparative evaluation of a new inhalation anesthetic, BAX-3224, and halothane in macaca speciosa 1975;54:144
Scamman FL. Fentanyl-O$_2$-N$_2$O rigidity and pulmonary compliance 1983;62:332
Scanlon JW, see Mendiola J
Scanlon TS III, see Benumof JL
  see Pease RD
Scarberry EH, see Hooks PJ
Scarpelli EM, Auld PAM, Goldman HS. Pulmonary disease of the fetus, newborn and child (book review) 1979;58:68
Schachter EN, see Kwon P
  see Lehnert BE
  see Rafferty TD
Schaffer DW, see Gross JB
  see Hartigan ML
Schaldach AL, see Shapiro HM
Schanus E, see Taylor CA
Schatz GC, see Berry AJ
Schehl DL, see Conner JT
  see Stirt JA
Scheijgrond H, see Starre Pvd
Scheijgrond HW, see van der Starre PJA
Scheinin BMA, see Rosenberg PH
Scheld HH, see v. Bormann B
Schemel WH. Is routine laboratory (SMA) screening justified? (correspondence) 1977;56:471
  Unexpected hepatic dysfunction found by multiple laboratory screening 1976;55:810
Schendel F, see Taylor CA
Schenk GK, see Freye E
Scher KS, see Pyles ST
Scherer K, see Hameroff SR
Schermer R, see Krantz EM
Schettini A, Stahurski B, Young HF, Rosner MJ. Plasma electrolytes and electrolyte excretion during osmotic and combined osmotic-loop diuresis in neurosurgery (abstract) 1982;61:213
Schick LM, see Cottrell WM
Schieber RA. Fundamentals of tracheal intubation (book review) 1984;63:706
  Lecture notes on fluid and electrolyte balance (book review) 1983;62:127
  see Boudreaux JP
Schiffer CA, see Lichtenfeld KM
Schiller NB, see Cahalan MK
Schimek F, Chapman CR, Gerlach R, Colpitts YH. Varying electrical acupuncture stimulation intensity: effects on dental pain-evoked potentials 1982;61:499
Schlereth H, see Lanz E
Schlobohm RM, see Gordon EP
Schmidt F, Jørgensen BC, Been H. Pain relief after modified radial mastectomy—premedication with a narcotic? (letter) 1984;63:372
  Jørgensen BC. The effect of metoclopramide on gastric contents after preoperative ingestion of sodium citrate 1984;63:841
Schmidt PJ, see Myhre BA
Schmuziger M, see Roskamm H
Schnapp M, May KS, North WC. Intravenous 2-chloroprocaine in treatment of chronic pain (letter) 1981;60:844
Schneider A, see Fyman PN
Schneider RC, see Kono K
  see Nieminen MT
  see Philbin DM
  see Tomichek RC
Schoeppel SL, Wilkinson C, Waters J, Meyers SN. Effects of myocardial infarction on perioperative cardiac complications 1983;62:493
Scholl ML, see Burchiel KJ
Schrader D, see Schuder RJ
Schuder RJ, Weis FR Jr, Markello R, White E, Schrader D. Diffusion hyperoxia following preoxygenation 1977;56:59
Schuette W, see Lees DE
Schuller JL, see Bovill JG
Schulte-Sasse U, Hess W, Markschies-Hornung A, Tarnow J. Combined effects of halothane anesthesia and verapamil on systemic hemodynamics and left ventricular myocardial contractility in patients with ischemic heart disease 1984;63:791
  see Hess W
Schultz RC. Outpatient surgery (book review) 1980;59:318
Schultz WW, see Naulty JS
Schuster DP, Snyder JV, Klain M. Comparison of venous admixture during high-frequency ventilation and conventional ventilation in oleic acid-induced pulmonary edema in dogs 1982;61:735
Schwam SJ. Pulmonary capillary wedge pressure (letter) 1982;61:805
  see Gold MI
Schwartz AJ, Dougal RM, Lee KW. Modification of oral airway as a bite block (letter) 1980;59:225
  Ellison N, Jobes DR, Parker EO, DeVore R. Errant guide wire: the problem (letter) 1982;61:717
  Ellison N, Ominsky AJ, Orkin FK. Advanced CPR—student, teacher, administrator, researcher 1982;61:629 1983;62:541
  Howse J, Ellison N, Widmer S. The gas line filter, a cause of hypoxia 1980;59:617
  Jobes DR, Ellison N. Rupture of pressurized plastic bags (letter) 1980;59:226
  Jobes DR, Levy WJ, Palermo L, Ellison N. External jugular cannulation—straight vs J-wire (abstract)

1981;60:275
  see Ellison N
Schweizer O, see Howland WS
  see Kahn RC
Sclabassi SE. Evaluation review (book review) 1984;63:626
Sclaroff A, see Owens WD
Scott DB, Chambers WA, Littlewood DG, Logan MR. Effect of added epinephrine on spinal anesthesia with lidocaine (abstract) 1981;60:275
  see Chambers WA
  see Ravindran RS
Scott DL, Ghia JN, Teeple E. Aphasia and hemiparesis following stellate ganglion block 1983;62:1038
Scott DS, see Ghia JN
Scott E, see Jones PIE
Scott JB, see Sawyer DC
Scott PV, see Levin KJ
Scovil JE, see Moffitt EA
Scruggs R, see Choi H
Scuderi PE, McLeskey CH, Comer PB. Emergency percutaneous transtracheal ventilation during anesthesia using readily available equipment 1982;61:867
  Prough D, Price JD, Comer PB. Cessation of pulmonary artery catheter-induced endobronchial hemorrhage associated with the use of PEEP 1983,62:236
Scurlock JE, Curtis BM. Dextran-local anesthetic interactions 1980;59:335
  see Moore DC
Seah CH, see Barretto C
Sear JW, see Prys-Roberts C
Sebel PS, Bovill JG. Cardiovascular effects of sufentanil anesthesia 1982;61:115
  Bovill JG. Fentanyl and convulsions (letter) 1983;62:858
  Bovill JG, Fiolet J, Touber JL, Philbin DM. Hormonal effects of sufentanil anesthesia (abstract) 1982;61:214
  Bovill JG, Wauquier A. Total narcotic anesthesia with sufentanil (abstract) 1981;60:276
  see Bovill JG
Sederberg J, Stanley TH, Reddy P, Liu WS, Port D, Gillmore S. Hemodynamic effects of butorphanol-oxygen anesthesia in dogs 1981;60:715
Seeman RG, see Burrows FA
Segal MS, see MacDonnell KF
Seifen A, see Lawson NW
Seifen AB, Ferrari AA, Seifen EE, Thompson DS, Chapman J. Pharmacokinetics of intravenous procaine infusion in humans 1979;58:382
Seifen EE, see Seifen AB
Seleny FL, see Levin RM
Sellers TD, see Lake CL
Sellick CL, see Stengert KB
Seltzer JL, Veloski J. Migration of physicians to and from anesthesiology (letter) 1983;62:702
  Doto JB, Jacoby J. Decreased arterial oxygenation during sodium nitroprusside administration for intraoperative hypertension (brief reports) 1976;55:880
  Hoarseness and Horner's syndrome after interscalene brachial plexus block 1977;56:585
  see Gerson JI
  Sodium nitroprusside for intraoperative hypertension (correspondence) 1977;56:749
  Veloski J. Changing specialties: do anesthesiologists differ from other physicians? 1982;61:504
  Cardiac arrest following pneumonectomy and pericardiotomy 1978;57:501
Selvin BL. Cancer chemotherapy: implications for the anesthesiologist 1981;60:425
Sendaydiego PM, see Cuasay OS
Sentker CR, see Bidwai AV
  see Hill GE
Seravalli EE, Lear E, Cottrell JE. Cell membrane fusion by chloroprocaine 1984;63:985
Serra M, see Baden JM
Serrins M, see Michaels I
Seski J, see Lichtiger B
Sessler S, see Chalon J
Sethna D, see Moffitt EA
Sethna DH, Gray RJ, Bussell JA, Raymond MJ, Matloff JM, Moffitt EA. Further studies on the myocardial metabolic effects of protamine sulfate following cardiopulmonary bypass (letter) 1982;61:476
  Gray RJ, Moffitt EA, Bussell JA, Raymond MJ, Conklin CM, Matloff JM. Dobutamine and cardiac oxygen balance in patients following myocardial revascularization 1982;61:917
  Moffitt EA, Bussell JA, Raymond MJ, Matloff JM, Gray RJ. Intravenous nitroglycerin and myocardial metabolism during anesthesia in patients undergoing myocardial revascularization 1982;61:828
  Moffitt EA, Gray RJ, Bussell JA, Matloff JM, Raymond MJ. Intravenous nitroglycerin and myocardial metabolism during anesthesia in patients undergoing myocardial revascularization (abstract) 1982;61:215
  Moffitt EA, Gray RJ, Bussell JA, Raymond MJ, Conklin C, Shell WE, Matloff JM. Cardiovascular effects of morphine in patients with coronary arterial disease 1982;61:109
  Moffitt EA, Gray RJ, Bussell J, Raymond M, Conklin C, Matloff JM. Effects of protamine sulfate on myocardial oxygen supply and demand in patients following cardiopulmonary bypass 1982;61:247
  see Moffitt EA
Seto K, Goto H, Hacker DC, Arakawa K. Right upper lobe atelectasis after inadvertent right main bronchial intubation 1983;62:581
Shabtai Y, see Bitterman H
Shackford SR, see Sise MJ
  Virgilio RW, Peters RM. Early extubation versus prophylactic ventilation in the high risk patient: a comparison of postoperative management in the prevention of respiratory complications 1981;60:76
Shader RI, see Divoll M
Shaffer MJ, see Lee DS
Shah DO, see Perry JC
Shah K, see Joseph MM
Shah NK, Kripke BJ, Sanzone CF, Cosman EB. Histological evaluation of cutaneous wound healing in presence of nitrous oxide in rats 1978;57:527
  see Kripke BJ
  see Radnay PA
Shah SC, see Samsi AB
Shanahan PT. Replantation anesthesia (letter) 1984;63:785
Shang W, see Rosen M
Shanks CA, Funk DI, Avram MJ, Henthorn TK. Gallamine administered by combined bolus and infusion 1982;61:847
  see Fragen RJ
  see Ramzan IM
  see Walker JS
Shanmugham M, see Mathru M
  see Rao TLK
Shantha TR. Introduction of anesthesia into infant by breast feeding (questions and answers) 1977;56:745
Shapiro BA, Harrison RA, Trout CA. Clinical application of respiratory care, second edition (book review) 1980;59:896
  Harrison RA, Walton JR. Clinical application of blood gases (book review) 1977;56:881
  see Harrison RA
Shapiro HM, Sanford TJ, Schaldach AL. Fiberoptic stylet laryngoscope and sitting position for tracheal intubation in acute superior vena caval syndrome 1984;63:161
  see Dunlop BJ

Shapiro HM—*continued*
  see Marsh ML
  Yoachim J, Marshall LF. Nitrous oxide challenge for detection of residual intravascular pulmonary gas following venous air embolism 1982;61:304
Shapiro LA, Hoffman S, Jedeikin R, Kaplan R. Single-injection epidural anesthesia with bupivacaine and morphine for prostatectomy 1981;60:818
Shapiro S, see Dolan PF
Sharma GP, see Minuck M
Sharp CW, It's no laughing matter (editorial) 1979;58:73
Sharrick NE. Inadvertent "3-in-1 block" following injection of the lateral cutaneous nerve of the thigh 1980;59:887
Shaw BW, see Martin DJ
Shaw CL, see Hill GE
Shaw LM, see Gross JB
Shaw R, see Vieira E
Sheehan J, see Michaels I
Shell WE, see Sethna DH
Shenoy PN, Leaman DM, Field JM. Safety of short-term percutaneous arterial cannulation 1979;58:256
Shepard LS, Gelman S, Reeves JG, Oparil S. Humoral response of hypertensive patients to laryngoscopy (abstract) 1981;60:276
Shephard DAE. Accuracy, brevity, clarity: three principles of good medical writing (correspondence) 1976;55:893
Shepherd JT, Vanhoutte PM. The human cardiovascular system (book review) 1980;59:715
Shepherd RM, see Martz KV
Sherwin RP, see Kripke BJ
Sheskey MC, Rocco AG, Bizzarri-Schmid M, Francis DM, Edstrom H, Covino BG. A dose-response study for bupivacaine for spinal anesthesia 1983;62:931
Shiau HF, Hwang HS, Marx GF. Prevention of external kinking of extradural catheters 1977;56:865
Shibata S, see Carrier O
Shibutani K, see Komatsu T
  see Kubal K
  see Tsueda K
Shibuya J, see Albert CA
Shier NQ, see Michaels I
Shigezawa GY, see Ritter JW
Shilyansky G, see Manchanda VN
Shimizu H, see Kaieda R
  see Shimoji K
Shimoji K, see Kaieda R
  Shimzu H, Maruyama Y, Matsuki M, Kuribayashi H, Fujioka H. Dorsal column stimulation in man: facilitation of primary afferent depolarization 1982;61:410
Shin B, Joseph SI. Hyperglycemic hyperosmolar nonketotic coma following diazoxide, anesthesia and operation 1977;56:506
  see Dongre SS
  see Mackenzie CF
Shin Y, see Lees DE
Shinder SM, see Rosen MA
Shingu K, Eger EI II, Johnson BH. Hypoxia may be more important than reductive metabolism in halothane-induced hepatic injury 1982;61:824
  Eger EI II, Johnson BH. Hypoxia per se can produce hepatic damage without death in rats 1982;61:820
  Eger EI II, Johnson BH, Lurz FW, Hickey RF. MAC values of thiopental and fentanyl in rats 1983;62:151
  Eger EI II, Johnson BH, Lurz FW, Taber V. Effects of halothane, isoflurane, enflurane, thiopental, and fentanyl on blood gas values in rats exposed to hypoxia 1983;62:155
  Eger EI II, Johnson BH, Van Dyke RA, Lurz FW, Harper MH, Cheng A. Hepatic injury induced by anesthetic agents in rats 1983;62:140
  Eger EI II, Johnson BH, Van Dyke RA, Lurz FW, Cheng A. Effect of oxygen concentration, hypothermia, and choice of vendor on anesthetic-induced hepatic injury in rats 1983;62:146
  see Eger EI II
Shipley SB, see Drain CB
Shirley MA, see Roberts RB
Shirley PD, see Perschau RA
Shiroka A, Rah KH, Keenan RL. Bronchospasm during cardiopulmonary bypass 1982;61:538
Shiu G, see Cook DR
Shiwaku Y, Nagashima H, Duncalf RM, Duncalf D, Foldes F. Naloxone fails to antagonize halothane-induced depression of the longitudinal muscle of the guinea pig ileum 1979;58:93
Shnider SM, Levinson G. Anesthesia for obstetrics (book review) 1980;59:522
  see Abboud TK
  see Hicks JS
  see Hughes SC
  see Rolbin SH
  see Rosen MA
Shoemaker WC, see Waxman K
  Tavares BM. Physiology, monitoring and therapy of the critically ill patient (book review) 1978;57:154
Shokes LK, see Craft JB Jr
Short CE, Paddleford RR, McGrath CJ et al. Preanesthetic evaluation and management of malignant hyperthermia in the pig experimental model 1976;55:643
Shoshany G, see Monies-Chass I
Shoults DL, see Mitchell SA
Shoum S, Kahn RC, Carlon GC, Howland WS. A guide-wire technique for the replacement of Swan-Ganz catheters 1980;59:455
Shrivastava OP, Chatterji S, Kachhawa S, Daga SR. Calcium gluconate pretreatment for prevention of succinylcholine-induced myalgia 1983;62:59
Shulman M, see Ivankovich AD
Shulman MS, Brodsky JB, Colby T, Mark JBD. The relationship of $FiO_2$ to postoperative mortality in patients who have received bleomycin (abstract) 1984;63:274
  Brodsky JB. The A.D.E. system—a new anesthetic breathing system (abstract) 1984;63:273
Shumacker CA, see Viegas OJ
Shumway NE, see Mihm FG
Shuptrine JR, Auffant RA, Gal TJ. Cerebral and cardiopulmonary responses to high frequency jet ventilation in a model of brain and lung injury 1984;63:1065
Shwiry B, see Cottrell JE
  see Giffin JP
Sia RL, Boonstra S, Westra P, Haenen HTM, Wesseling H. An electroencephalographic study of 4-aminopyridine 1982;61:354
  Zandstra DF, Overbeek JJ. Continuous intravenous anesthesia with etomidate for $CO_2$ laser surgery of the larynx 1982;61:993
Sibbald W, see Dickinson GE
Siedl DC, Martin DE. Prolonged bradycardia after neostigmine administration in a patient taking nadolol 1984;63:365
Siegel D, see Amirdivani M
Siegel JH, Chodoff P. The aged and high risk surgical patient: medical, surgical and anesthetic management (book review) 1977;56:758
Siegle JH, Dewan DM, James FM III. Cerebral infarction following spinal anesthesia for cesarean section 1982;61:390
Sievenpiper TS, see Wharton RS
Sih IL, see Odoom JA
Siker ES, see Cottrell JE
Sikh SS, Dhulia PN. Recovery from general anesthesia: a simple and comprehensive test for assessment 1979;58:324

- Sill JC, see Baele PL
- Silvay G, Litwak RS, Lukban SB, Jurado RA. Left heart assist device: early clinical experiences with management of postperfusion low cardiac output 1977;56:402
- Silver DJ, Dunsmore RH, Dickson CM. Spinal anesthesia for lumbar disc surgery: review of 576 operations 1976;55:550
- Silverberg GD, see Merrill DG
- Simko G, see Lanz E
- Simodynes E. Preoperative shock secondary to severe hypokalemia and hypocalcemia from recreational enemas 1981;60:762
- Simon DL, Carron H, Rowlingson JC. Treatment of bladder pain with transsacral nerve block 1982;61:46
- Simon R, see Chalon J
- Simpson FA, see Smith DJ
- Simpson PJ, see Durkin MA
- Simpson R, see Walton B
- Sims JK. A modification of landmarks for infraclavicular approach to brachial plexus block 1977;56:554
- Sinchioco CS, see McKenzie R
- Singer MM. Intermittent mandatory ventilation in the treatment of patients with chronic obstructive pulmonary disease (correspondence) 1975;54:119
- Singh P, see Ford DJ
- Singh-Amaranath AV, see Amaranath L
- Singler RC. Alcohol neurolysis of sciatic and femoral nerves 1981;60:532
- Sinno H, see Baraka A
- Siqueira EB, see Behnia R
- Sise MJ, Shackford SR, Peters RM, Virgilio RW. Serum oncotic pressure and oncotic-hydrostatic pressure differences in critically ill patients 1982;61:496
- Sison OS, see Garde JF
- Sitar DS, see Biehl DR
  - see Gregory GA
- Sittipong R, see Rorie DK
- Sivakumaran C, Ramanathan S, Chalon J, Satyanarayana T, Turndorf H. Spread of epidural anesthetics and uterine contractions (abstract) 1981;60:277
  - Ramanathan S, Chalon J, Turndorf H. Uterine contractions and the spread of local anesthetics in the epidural space 1982;61:127
- Sivarajan M, Amory DW, Everett GB, Buffington C. Blood pressure, not cardiac output, determines blood loss during induced hypotension 1980;59:203
  - Lane PE, Miller EV, Liu P, Herr G, Willenkin R, Winter P, Hardy CA, Mulroy MF. Performance evaluation: continuous lumbar epidural anesthesia skill test 1981;60:543
  - Miller E, Hardy C, Herr G, Liu P, Willenkin R, Cullen B. Objective evaluation of clinical performance and correlation with knowledge 1984;63:603
  - see Colley PS
- Sjöstrand UH, Eriksson IA. High rates and low volumes in mechanical ventilation—not just a matter of ventilatory frequency 1980;59:567
  - see Borg U
  - see Bunegin L
  - see Eriksson IA
  - see Koller ME
  - see Malina JR
  - see Rawal N
- Skarvan K. Cardiac tamponade and transmural myocardial pressures (letter) 1984;63:93
- Sklar GS, Alfonso AE, King BD. An unusual problem in nasotracheal extubation (brief reports) 1976;55:302
- Skourtis HT, see Balamoutsos NG
- Skupski JN, see Alexander GD
- Slater EE, see Kono K
- Slattery JT, see Bell LE
  - see Freund PR
- Slaughter RL, see McNamara PJ
- Slawson KB, see Davie IT
- Slogoff S, Girgis KZ, Keats AS. Etiologic factors in neuropsychiatric complications associated with cardiopulmonary bypass 1982;61:903
  - see Henling CE
- Slonim NB, Hamilton LH. Respiratory physiology, fourth edition (book review) 1982;61:73
- Smagalski G, see Bishay EG
- Small EW, see Campbell RL
- Smalley S, see Edde RR
- Smedstad K, see Morison DH
- Smith BE, Gabel RA, Marseglia JJ Jr, Farese G. Computer programs for acid-base variables (letter) 1982;61:475
  - Hess DG. Mechanism of ephedrine's activity in the pregnant ewe (abstract) 1981;60:278
- Smith CA. Management of patient with hypokalemia on diuretic therapy (questions and answers) 1976;55:276
- Smith CM, see Maze M
  - see Spiss CK
- Smith DB, Clark RB, Stephens SR et al. Physostigmine reversal of sedation in parturients 1976;55:478
- Smith DE, see Hobelmann CF Jr
- Smith DF, see Dasta JF
- Smith DJ, Rushin JM, Urquilla PR, Rhee CW, Yoon HJ, Simpson FA, Srichomkuan T, Lee HS, Knapp RB. Cardiovascular effects of benzquinamide 1979;58:189
- Smith DS, Gutsche BB. Amphetamine abuse and obstetrical anesthesia (letter) 1980;59:710
  - see Bruno LA
- Smith G, see Hornbein TF
  - see Hunt PCW
- Smith GA, Castresana MR, Mandel SD. Ventilatory management of tracheomalacia utilizing high-frequency jet ventilation 1983;62:538
- Smith H Jr, see Pratilas V
- Smith IE, see Ravindran RS
- Smith JD, see Hirshman CA
  - see Kingston HGG
- Smith KH, see Hornbein TF
- Smith LD, see Gross JB
- Smith LR, see Gelman S
  - see Reves JG
  - see Samuelson PN
  - see Tosone SR
- Smith M, see Cook TL
  - see Smith RA
- Smith NJ, see Linde HW
- Smith NT. Case history number 98: hypotension following cardiopulmonary bypass (comment) 1977;56:723
  - Dec-Silver H, Sanford TJ Jr, Westover CJ Jr, Quinn ML, Klein F, Davis DA. EEGs during high-dose fentanyl-, sufentanil-, or morphine-oxygen anesthesia 1984;63:386
  - Ingels NB Jr, Daughters GT II, Wexler L. Contribution of asynergic contraction to halothane-induced myocardial depression 1980;59:178
  - Miller RD, Corbascio AN. Drug interactions in anesthesia (book review) 1981;60:621
  - Quinn ML, Flick J, Fukui Y, Fleming R, Coles JR. Automatic control in anesthesia: a comparison in performance between the anesthetist and the machine 1984;63:715
  - see Burchiel KJ
  - see Calverley RK
  - see Eger EI II
  - see Fukui Y
  - see Gravenstein JS
  - see Jackson SH
  - see Saidman LJ
  - see Storms LH
- Smith PC, see Berryhill RE
- Smith PH, see Kim JW
- Smith R, see Harcus AW
- Smith RA, Paton WDM. The anesthesia effect of oxygen 1976;55:734
  - see Gooding JM
  - Smith M, Eger EI II, Halsey MJ, Winter

Smith RA—*continued*
  Smith M—*continued*
  PM. Nonlinear antagonism of anesthesia in mice by pressure 1979;58:19
Smith RB. Plasma concentration of lidocaine after endotracheal spray (correspondence) 1976;55:116
  see Babinski MF
  see Hoff BH
  see Koller ME
  see Waterman PM
Smith RH, Kano T, Cowan GSM, Barber RE. Electroanesthesia (EZ) studies: current applications to human volunteers to produce general and local anesthesia 1977;56:678
  see Kano T
Smith RL, see Bevan DR
Smith RM. Anesthesia for infants and children, 4th ed (book review) 1981;60:70
  Pediatric anesthesia in perspective, Sixteenth Annual Baxter-Travenol Lecture 1978;57:634
  see Koka RV
  see Sudhir KG
Smith TC, see Domino KB
  see Gross JB
  see Johnstone RE
Smith WS, see Moss J
Smits J, see Zegveld C
Smuckler EA, see Fassoulaki A
Snider MT, see Morita S
Snow JC, Kripke BJ, Norton ML et al. Corneal injuries during general anesthesia 1975;54:465
  Manual of anesthesia (book review) 1978;57:291
  Norton ML, Saluja TS et al. Fire hazard during $CO_2$ laser microsurgery on the larynx and trachea (brief reports) 1976;55:146
  Pre-and-post anesthetic use of atropine in patients with glaucoma (questions and answers) 1976;55:461
Snowdon SL. Hazards of narrow bore tubing in anesthesia machines (letter) 1984;63:92
Snyder JV, see Schuster DP
Sobczak OM. Use of ketamine in pediatric dentistry 1975;54:248
Sodeyama O, see Fukunaga AF
Sohn YJ, see Booij LHDJ
  see Roizen MF
  Succinylcholine, avoidance of side effects (questions and answers) 1975;54:637
  The effect of repeated doses of succinylcholine on serum potassium in patients with renal failure (guest discussion) 1975;54:748
Sohn YZ, Hong JC, Katz RL. Antiarrhythmic and hemodynamic responses to adenosine triphosphate during infusion of epinephrine in dogs anesthetized with halothane 1982;61:423
  Katz RL. Interaction of halothane and antibiotics on isometric contractions on rat-heart muscle 1977;56:515
Sokoll M, see Choi W
Sokoll MD. Cardiac decompensation during enflurane anesthesia in a patient with myotonia atrophica (case history comment) 1976;55:436
  Kassell N, Davies LR. Cardiovascular effects of deep barbiturate anesthesia (abstract) 1980;59:559
  Ketamine interaction with neuromuscular blocking agents in the phrenic nerve-hemidiaphragm preparation of the rat (comment) 1978;57:243
  see Faust DK
  see Rubbo JT
  see Stullken EH Jr
Solanki D, see Priano LL
Solanki DR, Suresh M, Ethridge HC. The effects of intravenous cimetidine and metoclopramide on gastric volume and pH 1984;63:599
Sold M. More on protamine dosage (letter) 1984;63:783
Soliman MG, Tremblay NA. Nerve block of the penis for postoperative pain relief in children 1978;57:495
Solod E, see Rosenberg M
Soltis JJ, Gandolfi AJ. Detection of fluorinated anesthetic metabolites by sodium fusion 1980;59:61
  see Blitt CD
Somerville GM, see Ravindran RS
Sommer U, see Lanz E
Soper LE, see Vitez TS
Soper PG, see Vitez TS
Sørensen O, Eriksen S, Hommelgaard P, Viby-Mogensen J. Thiopental-nitrous oxide-halothane anesthesia and repeated succinylcholine 1980;59:686
Soroker D, Barzilay E, Konichezky S, Bruderman I. Respiratory function following premedication with droperidol or diazepam 1978;57:695
Sosis M, Bodner A, Admad I. Management of cholinesterase inhibitor poisoning in obstetrics (letter) 1983;62:1135
  Normann E. Further considerations in unusual disconnections (letter) 1983;62:1134
Soter NA, see Fahmy NR
Souron RJ, see Pinaud MJL
Southorn PA, MacKenzie RA, Gould AB Jr, Offord KP. Routine end-tidal carbon dioxide tension ($P_{ET}CO_2$) monitoring in the immediate postoperative period (abstract) 1984;63:275
  see Baele PL
Spackman TN. Low thermodilution cardiac output due to an intracatheter septal defect (letter) 1984;63:963
Spaepen M, Berryman JR, Fencl V. Nebulizer contamination (correspondence) 1978;57:749
Spaepen MS, Berryman JR, Bodman HA, Kundsin RB, Fencl V. Prevalence and survival of microbial contaminants in heated nebulizers 1978;57:191
Spaeth EE, see Link WJ
Spagnuolo S, see Grundy BL
Spain J, see Wheeler AS
Spain JA, see Reves JG
Sparks DL, Corssen G, Aizenman B et al. Further studies of the renal mechanisms of ketamine-induced anesthesia in the Rhesus monkey 1975;54:189
Speers L, see Koblin DD
Sperling M, see Blumenberg D
Spiegel EH, see Lind GL
Spielholz NL, see Wang BC
Spierdijk J,
  see Moore DC
  see Nauta J
Spiro SR. Pain and anxiety control in dentistry (book review) 1981;60:847
Spiss CK, Maze M, Smith CM. α-Adrenergic responsiveness correlates with epinephrine dose for arrhythmias during halothane anesthesia in dogs 1984;63:297
  see Berry AJ
  Smith CM, Maze M. Halothane-epinephrine arrhythmias and adrenergic response after chronic imipramine treatment in dogs (abstract) 1984;63:276
  Smith CM, Maze M. Halothane-epinephrine arrhythmias and adrenergic responsiveness after chronic imipramine administration in dogs 1984;63:817
Spitznagel EL Jr, see Brown FF III
Spodick DH, see List WF
Spoerel WE, see Bain JA
  see Lampe KM
Spooner RB. Hospital electrical safety simplified (book review) 1980;59:958
  Oxygen analyzers unreliable as disconnection alarms (letter) 1984;63:962
Sprague DH. Faulty side port/hemostasis valve catheter to sheath adapter (letter) 1984;63:168
  Kim DI. Pseudohypertension due to Mönckeberg's arteriosclerosis 1978;57:588

  Norfleet EA. Pseudo resistance to nitroprusside (letter) 1980;59:518
  see Merritt JC
  see Sarwar H
  Wolf S. Enflurane seizures in patients taking amitriptyline 1982;61:67
Spray TL, see Christian CM
Sprigge JS, see Wynands JE
  Wynands JE, Whalley DG, Bevan DR. Townsend GE, Nathan H, Patel YC, Srikant CB. Fentanyl infusion anesthesia for aortocoronary surgery: plasma levels and hemodynamic response 1982;61:972
Springstead J, see Rosenberg H
Spurgeon MJ. Apparent resistance to succinylcholine 1979;58:57
Srichomkuan T, see Smith DJ
Srikant CB, see Sprigge JS
  see Wynands JE
Sriwatanakul K, see Weis OF
Stackhouse J, see Fyman PN
Stadt HH, see de Bruijin NP
Stafford M, see Cartwright P
Stahurski B, see Schettini A
Stamm SJ, see Morray JP
Standaert FG, Dretchen KL. Cyclic nucleotides in neuromuscular transmission 1981;60:91
Stanec A, Heyduk J, Stanec G, Orkin LR. Tetanic fade and post-tetanic tension in the absence of neuromuscular blocking agents in anesthetized man 1978;57:102
  Stanec G. Adductor pollicis monitor (letter) 1984;63:1141
  Stanec G, Baker T. Correlation between anticurare activity of tetanic stimulation and neostigmine in anesthetized man 1981;60:175
  Stanec G. The adductor pollicis monitor—apparatus and method for the quantitative measurement of the isometric contraction of the adductor pollicis muscle 1983;62:602
Stanec G, see Stanec A
Stanford W, see Downs JB
Stanley TH, Bidwai AV, Lunn JK, Hodges MR. Cardiovascular effects of nitrous oxide during meperidine infusion in the dog 1977;56:836
  Cardiovascular effects of metocurine during enflurane anesthesia in man 1978;57:540
  Cazalaa JA, Atinault A, Coeytaux R, Limoge A, Louville Y. Transcutaneous cranial electrical stimulation decreases narcotic requirements during neurolept anesthesia and operation in man 1982;3:863
  Hill E, Portas MR et al. Neutrophil chemotaxis during and after general anesthesia and operation 1976;55:668
  Hill GE, Hill HR. The influence of spinal and epidural anesthesia on neutrophil chemotaxis in man 1978;57:567
  Isern-Amaral J, Lathrop GD. Urine norepinephrine excretion in patients undergoing mitral or aortic valve replacement with morphine anesthesia 1975;54:509
  Leysen J, Niemegeers CJE, Pace NL. Narcotic dosage and central nervous system opiate receptor binding 1983;62:705
  Limoge A, Gazalaa J, Louville Y. Transcutaneous cranial electrical stimulation decreased narcotic requirements during neuroleptanesthesia and operation in man (abstract) 1982;61:216
  Liu WS. Cardiovascular effects of meperidine-N$_2$O anesthesia before and after pancuronium 1977;56:669
  Lunn JK. Anticoagulants and continuous epidural anesthesia (letter) 1980;59:394
  Lunn JK, Liu WS, Gentry S, Olsen D. Peripheral vascular and direct cardiac effects of digoxin in the calf 1980;59:11
  see Aldrete JE
  see Andriano KP
  see Bailey PL
  see Bennett GM
  see Bidwai AV
  see Bruce DL
  see Brunner EA
  see de Lange S
  see Hill GE
  see Kawamura R
  see Liu WS
  see Loeser EA
  see Lunn JK
  see Meuleman TR
  see Nauta J
  see Pace NL
  see San Juan AC Jr
  see Sederberg J
  see Webster LR
  see Westenskow DR
  Zikria BA. The surface tension of upper airway secretions in patients with and without respiratory disease 1975;54:602
Stanley VF, see Samuelson RJ
Stanski DR, see Booij LHDJ
Stanton-Hicks M. Epidural antibiotics with prolonged catheterization (questions and answers) 1976;55:132
  International anesthesiology clinics regional anesthesia: advances and selected topics (book review) 1979;58:162
Star AM, see Bruno LA
Stark AH, see Storms LH
Stark DC. Practical points in anesthesiology (book review) 1981;60:233
Starkweather JA, see Cook TL
Starr A, see Harlan BJ
Starre Pvd, Scheijgrond H. Ketanserin, a specific 5 HT$_2$-receptor blocker, in treatment of postoperative hypertension following coronary artery bypass surgery (abstract) 1982;61:216
Staudte HW, see Lanz E
Steczyn MV, see Levin RM
Stedman DH, see Corbett TH
Steen PA, Bromage PR, Camporesi EM. Duplication and fragmentation in publication (letter) 1982;61:1024
Steen SN, see Lippmann M
  see Ramamurthy S
Steen SS, see Lippmann M
Stefani SJ, see Hughes SC
Steffey EP, Johnson BH, Eger EI II, Howland D Jr. Nitrous oxide-effect on accumulation rate and uptake of bowel gases 1979;58:405
  see Gibbons RT
  Woliner M, Howland D. Evaluation of an isoflurane vaporizer: the Cyprane Fortec 1982;61:457
Steffins J, see Wong KC
Stehling LC, see Jones DJ
  see Patil VU
  Zauder HI. Anesthetic implications of congenital anomalies in children (book review) 1981;60:541
Steidl LJ, Fromme GA, Danielson DR. Lumbar versus thoracic epidural morphine for post-thoracotomy pain (abstract) 1984;63:277
Stein J, see Lampe KM
Steinbach RB, see Dolan PF
Steinbrook RA, Carr DB, Datta S, Naulty JS, Lee C, Fisher J. Dissociation of plasma and cerebrospinal fluid beta-endorphin-like immunoactivity levels during pregnancy and parturition 1982;61:893
Steiner J, see Bochner F
Steinhaus JE. A milestone in anesthesiology: a book award (editorial) 1978;57:159
Stengert KB, see Reitan JA
  Sellick CL, Lazerson J. Halothane-induced platelet dysfunction (abstract) 1982;61:217
Stephen CR, see Owens WD
  see Wilson SL
Stephens SR, see Smith DB
Stephenson LW, see Ellison N
Stern IJ, see Wallin RF
Stern RC, see Lough MD
Stern SB, see Neuman GG
Sternecker CL, see Losasso AM

- Steude GM, see Lane GA
- Stevens WC. Anesthetic management 1976;55:622
  - Changes in blood chemistries following prolonged enflurane anesthesia (guest discussion) 1976;55:549
  - see Comstock MK
  - see Eger EI II
  - see Roizen MF
  - see Wade JG
  - see White AE
- Stevenson IH, see Crooks J
- Stevenson JG, see Morray JP
- Steward DJ, Izukawa T. Congenital complete heart block (letter) 1980;59:81
  - Management of epiglottitis in children (guest discussion) 1975;54:624
  - Manual of pediatric anesthesia (book review) 1980;59:167
  - see Jones PIE
- Stewart HC, see Vickers MD
- Stewart MS, Reich JH, Rosenblatt RM. Chronic pain in a patient with a somatization disorder 1984;63:163
- Stewart RD. Procedures and techniques in emergency medicine (book review) 1983;62:863
- Stieglitz P, see Dupre LJ
- Stiff JL, Munch DF, Bromberger-Barnea B. Hypotension and respiratory distress caused by rapid infusion of mannitol or hypertonic saline 1979;58:42
- Stiffel P, Hameroff SR, Blitt CD. Electrode type and placement during train-of-four affects assessment of neuromuscular blockade (abstract) 1980;59:560
- Stiller PL. Drug disposition in anesthesia (book review) 1983;62:622
- Stilz RJ, Carron H, Sanders DB. Case history number 96: reflex sympathetic dystrophy in a 6-year-old: successful treatment by transcutaneous nerve stimulation 1977;56:438
- Stine L, see Abboud T
- Stirt AT, Sullivan SF. Aminophylline 1981;60:587
- Stirt JA. Aminophylline is a diazepam antagonist 1981;60:767
  - Anesthetic problems in Rubenstein-Taybi syndrome 1981;60:534
  - Berger JM, Ricker SM, Sullivan SF. Aminophylline pharmacokinetics and cardiorespiratory effects during halothane anesthesia in experimental animals 1980;59:186
  - Berger JM, Ricker SM, Sullivan SF. Arrhythmogenic effects of aminophylline during halothane anesthesia in experimental animals 1980;59:410
  - Berger JM, Roe SD, Ricker SM, Sullivan SF. Halothane-induced cardiac arrhythmias following administration of aminophylline in experimental animals 1981;60:517
  - Berger JM, Roe SD, Ricker SM, Sullivan SF. Safety of enflurane following administration in experimental animals 1981;60:871
  - Berger JM, Roe SD, Ricker SM, Sullivan SF. Cardiovascular effects of ketamine following administration of aminophylline in dogs 1982;61:685
  - Berger JM, Sullivan SF. Lack of arrythmogenicity of isoflurane following administration of aminophylline in dogs 1983;62:568
  - Frantz RA, Gunz EF, Conolly ME. Anesthesia, catecholamines, and hemodynamics in autonomic dysfunction 1982;61:701
  - Kaufman RD. Hazard associated with armored endotracheal tube (correspondence) 1978;57:381
  - Murray AL, Katz RL, Schehl DL, Lee C. Atracurium during halothane anesthesia in humans 1983;62:207
  - see Berger JM
  - see Katz RL
  - see Rosko TJ
  - Succinylcholine in congenital pyruvate kinase deficiency 1982;61:620
- Stobie G, see Lees DE
- Stock MC. On unusual values of PAD and PAOP (letter) 1984;63:89
- Stockard JL, see Burchiel KJ
- Stockman A, see Zegveld C
- Stoelting RK. A dosage nomogram for sodium nitroprusside-induced hypotension under anesthesia (guest discussion) 1975;55:574
  - Allergic reactions during anesthesia 1983;62:341
  - Attenuation of blood pressure response to laryngoscopy and tracheal intubation with sodium nitroprusside 1979;58:116
  - Balanced anesthesia (questions and answers) 1976;55:907
  - Blood pressure and heart rate changes during short-duration laryngoscopy for tracheal intubation: influence of viscous or intravenous lidocaine 1978;57:197
  - Circulatory changes in patients with coronary artery disease following thiamylal-succinylcholine and tracheal intubation 1976;55:232
  - Circulatory response to laryngoscopy and tracheal intubation with or without prior oropharyngeal viscous lidocaine 1977;56:618
  - Comparison of gallamine and atropine as pretreatment before anesthetic induction and succinylcholine administration 1977;56:493
  - Creasser CW, Martz RC. Effect of cocaine administration on halothane MAC in dogs 1975;54:422
  - Gas embolism during encephalography (case history comment) 1976;55:143
  - Gastric fluid pH in patients receiving cimetidine 1978;57:675
  - Gastric fluid volume and pH after fentanyl, enflurane, or halothane-nitrous oxide anesthesia with or without atropine or glycopyrrolate 1980;59:287
  - Gastric function (letter) 1980;59:807
  - Heart rate slowing and junctional rhythm following intravenous succinylcholine with and without intramuscular atropine preanesthetic medication 1975;54:705
  - Influence of barbiturate anesthetic induction on circulatory responses to morphine 1977;56:615
  - Influence of pancuronium or *d*-tubocurarine on circulatory responses during thiamylal-$N_2O$ halothane anesthesia 1976;55:485
  - McCammon RL, Hilgenberg JC. Changes in blood pressure with varying rates of administration of *d*-tubocurarine 1980;59:697
  - Nawaf K. Enflurane vaporizer accuracy with nitrous oxide mixtures (letter) 1979;58:440
  - Neurofibromatosis, renal hypertension, and cardiac dysrhythmias (case history comment) 1975;54:543
  - Opiate receptors and endophins their role in anesthesiology 1980;59:874
  - Peterson C. Adverse effects of increased succinylcholine dose following *d*-tubocurarine pretreatment 1975;54:282
  - Peterson C. Circulatory changes during anesthetic induction: impact of *d*-tubocurarine pretreatment, thiamylal, succinylcholine, laryngoscopy, and tracheal lidocaine 1976;55:77
  - Peterson C, Madura JA. Circulatory responses and halothane concentrations during gastric or gallbladder traction with and without neuromuscular blockade 1976;55:388
  - Plasma lidocaine concentrations following subcutaneous or submucosal epinephrine-lidocaine injection 1978;57:724
  - see Hilgenberg JC
  - see McCammon RL
  - see McGammon RL

  see Nawaf K
  see Ullman JI
  see Viegas O
  see Wagner DL
  see Young SR
  Sustained high inspired $P_{O_2}$ without toxic sequelae (case history comment) 1976;55:590
  Urine norepinephrine excretion in patients undergoing mitral or aortic valve replacement with morphine anesthetics (guest discussion) 1975;54:516
  Ventilatory arrest after meperidine 1977;56:727
  Viegas O, Campbell RL. Sodium nitroprusside-produced hypotension during anesthesia and operation in the head-up position 1977;56:391
Stokes DW. Murphy's law and humidification (letter) 1983;62:461
Stokstad ELR, see Koblin DD
Stoll M, see Nagashima H
Stone DR, Downs JB, Paul WL, Perkins HM. Adult body temperature and heated humidification of anesthetic gases during general anesthesia 1981;60:736
Stone JG, Hoar PF, Calabro JR, DePetrillo MA, Bendixen HH. Afterload reduction and preload augmentation improve the anesthetic managment of patients with cardiac failure 1980;59:737
  Hoar PF, Faltas AN, Khambatta HJ. Nitroprusside and mitral stenosis 1980;59:662
  see Khambatta HJ
Stone WJ, see Wood M
Stool S. Fiberoptic endoscopy in anesthesia (book review) 1984;63:471
Stoops CA, see Ravindran RS
  see Viegas OJ
Stoops CM. Acute hyperkalemia associated with massive blood replacement (letter) 1983;62:1044
  see Ravindran R
Storms LH, Stark SH, Calverley RK, Smith NT. Psychological functioning after halothane or enflurane anesthesia 1980;59:245
Strauch MJ. Pharmacology of respiratory therapy medications (book review) 1979;58:533
Strausburg BJ, see Ravindran RS
Strobel GE Jr. Effect of halothane on isometric twitch and tetanus response and the associated heat production in striated muscle of frogs (guest discussion) 1975;54:535
Strong E, see Yanagida H
Strong S, see Gelman S
Strum G, see v. Bormann B
Strunin L, Davies JM, Corrall IM. A perspective on halothane-induced hepatoxicity (letter) 1983;62:540
  see Bird TM
Strupta J, see Knill R
Stullken EH Jr, Sokoll MD. Anesthesia and subarachnoid intracranial pressure 1975;54:494
  Sokoll MD. The effects of heparin on recovery from ischemic brain injuries in cats 1976;55:683
Sturgeon CL Jr, Douglas ME, Downs JB, Dannemiller FJ. PEEP and CPAP: cardiopulmonary effects during spontaneous ventilation 1977;56:633
Su JY, Kerrick GL, Hill SA. Effects of diethyl ether and nitrous oxide on functionally skinned myocardial cells of rabbits 1984;63:451
  see Caplan RA
Subaiya C, see Youngberg JA
Subaiya L, Rege A, Weng JT, George W, Texidor M. The influence of isoflurane on plasma beta-endorphin immunoreactivity (abstract) 1984;63:278
Sudan NK, Michaels I, Barash PG. Continuous narcotic infusions for pediatric patients: a reality? (abstract) 1984;63:279
Sudhir KG, Smith RM, Hall JE et al. Intraoperative awakening for early recognition of possible neurologic sequelae during Harrington-rod spinal fusion 1976;55:526
Suer SF, see Aukburg SJ
Suffecool SL, see Blanck TJJ
Sullivan JA, see Moffitt EA
Sullivan S, see Wong KC
Sullivan SF. Case history number 98: hypotension following cardiopulmonary bypass (guest discussion) 1977;56:723
  see Berger JM
  see Ritter JW
  see Rosko TJ
  see Stirt JA
Sumi SM, see Barsa JE
Summary JJ, see Moore WE
Summer WR, see Furman WR
Sumner E, see Kaufman L
Sumpter R, see Kaplan JA
Sunder N, see Ali HH
  see Basta SJ
  see Fahmy NR
Sung YF, Kutner MH, Cerine FC, Frederickson EL. Comparison of the effects of acupuncture and codeine on postoperative dental pain 1977;56:473
  see Ghani GA
Suratt PM, see Gal TJ
Suresh M, see Solanki DR
Surks SN, see Kopmann AF
Suseela M, see Rao TLK
Susuki D, see Aldrete JA
Sutcliffe AJ. Modified Dawkins epidural indicator (letter) 1979;58:350
Suwa K, see Yanagida H
Suzukawa M, Michaels IAL, Ruzbarsky J, Kopriva CJ, Kitahata LM. Use of isoflurane during resection of pheochromocytoma 1983;62:100
  see Collins JG
Sweet JB, see Gelfman SS
Swen J, see Gencarelli PJ
Swerdlow M. Relief of intractable pain (book review) 1979;58:69
Swierk P, see Umlas J
Sy WP. Ulnar nerve palsy possibly related to use of automatically cycled blood pressure cuff 1981;60:687
Sykes MK, Vickers MD, Hull CJ. Principles of clinical measurement (book review) 1981;60:847
Sylvester JT, see Furman WR
Szyfelbein SK, see Martyn JAJ
Tabaddor K, see Frost EAM
Tabatabai M. Calcium regulation by calcium antagonists (book review) 1984;63:547
  Degradation of endogenous opioids—its relevance in human pathology and therapy (book review) 1984;63:547
Taber V, see Shingu K
Tabsh KMA, see Murad SHN
Taff RH, see Umlas J
Taillefer J, see Hardy JF
Takacs FA. Paravertebral sympathetic block (correspondence) 1978,57:145
  Single-needle lateral approach for lumbar sympathetic block (correspondence) 1976;55:454
Takahashi T, see Mayumi T
Takeshita H, see Fukuda S
  see Kaieda R
  see Sari A
Takeya H, see Yamamura T
Takkunen O, see Salmenperä M
Takman BH, see Adams HJ
Talbott GD, see Farley WJ
Tallman RD, see Rosenblatt RM
Talmage EA. Shearing hazard of intraarterial Teflon catheters (brief reports) 1976;55:597
Tammisto T, see Erkola O
Tan LT, Tan MYC, Veith I. Acupuncture therapy: current chinese practice, 2nd ed (book review) 1977;56:172
Tan MYC, see Tan LT
Tan RN, see Abouleish E
Tan ST, see Aldrete JA
Tanaka I, see Juang MS
Tang CK, Chalon J, Markham JP, Ramanathan S, Turndorf H. Exposure of sires to enflurane

Tang CK—*continued*
affects learning function of murine progeny 1984;63:729
Dwarakanath R, Ramanathan S, Chalon J, Fischgrund GK, Turndorf H. A percolator vaporizer heated by reaction of neutralization of lime by carbon dioxide 1981;60:146
see Chalon J
see Paspa P
Tanguturi S, Capan LM, Patel K, Turndorf H. A new double-lumen tube adaptor 1980;59:507
Tanifuji Y, Eger EI II. Brain sodium, potassium, and osmolality: effects on anesthetic requirement 1978;57:404
Eger EI II. Effect of isoproterenol and propranolol on halothane MAC in dogs 1976;55:383
Eger EI II, Terrell RC. Some characteristics of an exceptionally potent inhaled anesthetic: thiomethoxyflurane 1977;56:387
Tank CK, see Chalon J
Tanner G. Pharmacokinetics of inhalation anesthetics: a three-compartment linear model 1982;61:587
Tannieres ML, Chelly J, Chaignon M, Derome P, Vourc'h G. Prostacyclin as an hypotensive agent during neurosurgery (abstract) 1984;63:280
Tantisira B, see McKenzie R
Tanz RD, Heskett T, Loehning RW, Fairfax CA. Comparative cardiotoxicity of bupivacaine and lidocaine in the isolated perfused mammalian heart 1984;63:549
Tarazi RC, see Estafanous FG
Tarhan S. Cardiovascular anesthesia and postoperative care (book review) 1982;61:958
see Cant WF
see Moffitt EA
Tarnow J, see Hess W
see Schulte-Sasse U
Tarrow AB, Erickson JC. Basic and clinical sciences in anesthesiology, ninth edition (book review) 1981;60:126
Tasch MD, see Ravindran RS
Tatekawa S, see Yukioka H
Yukoka H, Nishimura H, Frijimori M. New adaptor for intravascular electrocardiogram (letter) 1982;61:884
Taub HA, Eisenberg L. An evaluation of memory under regional anesthesia with IV lorazepam as a premedicant 1976;55:368
Tausk HC, Miller R, Roberts RB. Maintenance of body temperature by heated humidification 1976;55:719
see Miller R
Tavakoli M, Corssen G, Caruso FS. Butorphanol and morphine: a double-blind comparison of their parenteral analgesic activity 1976;55:394
Habeeb A. Two hazards of gas scavenging 1978;57:286
see Gooding JM
Tavares BM, Frey R. Acute care (book review) 1980;59:319
see Shoemaker WC
Tay CH, see Konchigeri HN
see Winnie AP
Taylor A, see Rogers K
Taylor CA, Lovrien R, Schanus E, Schendel F, Kreul JF. Erythrocyte abnormalities in survivors of malignant hyperthermia (abstract) 1981;60:278
Taylor FH, see Abouleish E
see McKenzie R
Teddy P, see Watson J
Teeple E, see Scott DL
Tehrani ML, see Weiss RR
Tejani NA, see Weiss RR
Tempesta E, see Ansari IA
TenEyck LG, see Colgan FJ
Teplick RS, Caldera DL, Gilbert JP, Cullen DJ. Benefit of elective intensive care admission after certain operations 1983;62:572
see Lebowitz PW
see Tomicheck RC
Terrell RC, see Koblin DD
see Tanifuji Y
Teske RH, see Adams HR
Texeira R, see Bennett MJ
Texidor M, see Subaiya L
see Youngberg JA
Tham MK, see Munson ES
Theiss D, see Lanz E
Theophanidis C, see Kaniaris P
Thiagarajah S, Girnar DS, Park K. Blood pressure monitoring using the superficial temporal artery and a Doppler ultrasonic flow detector 1979;58:526
Thibeault DW, Gregory GA. Neonatal pulmonary care (book review) 1981;60:848
Thisted RA, see Moss J
Thistlewood JM, see Dewan DM
Thomas DV. Saline with benzyl alcohol prevents pain of needle insertion (letter) 1984;63:883
Thomas JL, see Cooke JE
see Dodge TL
see Yakaitis RW
Thomas KC Jr, see Brückner J
see Burkett L
Thompson DR. The pharmacologic approach to the critically ill patient (book review) 1984;63:706
Thompson DS, see Lawson NW
see Seifen AB
Thompson GA, see Denson DD
Thompson GE. A rationale for high spinal anesthesia (abstract) 1980;59:561
Moore DC, Bridenbaugh LD, Artin RY. Abdominal pain and alcohol celiac plexus nerve block 1977;56:01
see Moore DC
Thompson M. Calcium transport by cardiac sarcoplasmic reticulum: modulation of halothane action by substrate concentration and pH 1981;60:390
see Blanck TJJ
Thompson PW, see Mushin WW
Thompson RL, see Gronert GA
Thompson TR, see Belani KG
Thomsen A. Bronchofiberscopic jet ventilation (letter) 1981;60:68
Thomson IR, Gerson JI, Allen FB. Vasodilation with nitroprusside and nitroglycerin (letter) 1982;61:887
see Mutch WAC
Thornton JA. Adverse reactions to anaesthetic drugs (book review) 1982;61:550
Thorpe DH. Opiate structure and activity—a guide to understanding the receptor 1984;63:143
Thurman BH, see de Jong RH
Tilson MD, see Barash PG
Tinker JH, see Backer CL
see Cant WF
see Hughes DR
Tio TO, see Abouleish E
Tjay HT, see Kraynack BJ
Tjovairi E, see Balamoutsos NG
Tobey RE, see Laflin MJ
see Mayhew JF
see Naulty JS
see Posner MA
Tobias R. Increased success with retrograde guide for endotracheal intubation (letter) 1983;62:366
Toda N, see Fukuda S
see Harioka T
Todd EP, see Debrand M
Todd MM, Morris PJ, Moss J, Philbin DM. Hemodynamic consequences of abrupt withdrawal of nitroprusside or nitroglycerin following induced hypotension 1982;61:261
Morris PJ, Philbin DM. Acute neurologic changes caused by nitroprusside-induced intracranial hypertension (abstract) 1980;59:561
Tomicheck RC, Rosow CE, Schneider RC, Moss J, Philbin DM. Cardiovascular effects of diazepam-fentanyl anesthesia in patients with coronary artery disease (abstract) 1982;61:217
Rosow CE, Philbin DM, Moss J, Teplick

RS, Schneider RC. Diazepam-fentanyl interaction—hemodynamic and hormonal effects in coronary artery surgery 1983;62:881
Tomlinson T, see Gattinoni L
Tompkins BM, Thompkins WJ, Loder E, Noonan AF. A computer-assisted preanesthesia interview 1980;59:03
Tompkins WJ, see Tompkins BM
Tondare AS, see Nadkarni AV
Toner W, see Johnston JR
Torchia MG, see Cote DD
Tormo VJ, see Visconti JA
Tornetta FJ. A comparison of droperidol, diazepam, and hydroxyzine hydrochloride as premedication 1977;56:496
  Droperidol premedication (correspondence) 1978;57:289
Toro-Matos A, Rendon-Platas AM, Avila-Valdez E, Villarreal-Guzman RA. Physostigmine antagonizes ketamine 1980;59:764
Torpey DJ. Thoracic anesthesia (book review) 1983;62:543
Torpey DJ Jr. Cardiac anesthesia. Volume 2, Cardiovascular pharmacology (book review) 1984;63:377
Tosone SR, Reves JG, Kissin I, Smith LR, Lell WA. Nifedipine and halothane interaction: hemodynamic depression in dogs (abstract) 1982;61:218
  Reves JG, Kissin I, Smith LR, Fournier SE. Hemodynamic responses to nifedipine in dogs anesthetized with halothane 1983;62:903
  see Reves JG
Touber JL, see Bovill JG
  see Sebel PS
Toung JK, see Alvaran SB
Toung TJK, see Chen CT
Townsend GE, see Ralley FE
  see Sprigge JS
  see Wynands JE
Townsley MI, see Weiskopf RB
Toyooka ET, see Zahed B
Trahey GE, see Hendrickx HHL
Tran B, see Yang E
Trapp LD. Dentistry and anesthesia (correspondence) 1978;57:751
  see Reder BS
Traynor CA, Van Dyke RA, Gronert GA. Phosphorylase ratio and susceptibility to malignant hyperthermia 1983;62:324
Traystman RJ, see Baskoff JD
  see Donegan J
  see Rogers MC
Tremblay NA, see Soliman MG
Tremper KK, see Choi H
  Zaccari J, Cullen BF, Hufstedler SM. Liquid–gas partition coefficients of halothane and isoflurane in perfluorodecalin, fluosol-DA, and blood/fluosol-DA mixtures 1984;63:690
Triantafillou A, see Kono K
  see Nieminen MT
Trichet B, see Vourc'h G
Triggs EJ, see Ramzan IM
Triner L, see Bernstein KJ
  see Vulliemoz Y
  see Walter F
Trousdale FR, see Benumof JL
Trout CA, see Shapiro BA
Troutman KC, see Reder BS
Trubuhovich RV. Management of acute intracranial disasters (book review) 1979;58:535
Trudell JR, see Cohen EN
Trudnowski RJ, Gessner JT. Gastric excretion of intravenously administered meperidine in surgical patients 1979;58:88
Trueblood S, see Rao CC
Trump BE, see Cowley RA
Trustman R, see Dubovsky SL
Tsakona H, see Balamoutsos NG
Tsuchida H, see Dohi S
Tsueda K, Debrand M, Zeok SS, Wright BD, Griffin WO. Obesity supine death syndrome: reports of two morbidly obese patients 1979;58:345
  Dubick MN, Wright BD, Sachatello CR. Intraoperative hyperthermic crisis in two children with undifferentiated lymphoma 1978;57:511
  see Debrand M
  see Zeok SS
  Shibutani K, Lefkowitz M. Postoperative ventilatory failure in an obese, myopathic woman with periodic somnolence: a case report 1975;54:523
Tsuji T, see Fukuda S
Tubino PJ, see Couto da Silva JM
Tung AS, see Albin MS
  see Grundy BL
Tuohy GF, see Fibuch EE
Tuominen MK, see Kalso EA
Turgeon LR, see Hupert C
Turkey K, see Roizen MF
Turndorf H, see Amirdivani M
  see Azar I
  see Bernhard WN
  see Buffington DW
  see Capan LM
  see Chalon J
  see Cottrell JE
  see O'Meara JB
  see Paegle RD
  see Paspa P
  see Ramanathan S
  see Satyanarayana T
  see Sivakumaran C
  see Tang CK
  see Tanguturi S
  see Wang BC
  see Yost LC
  Urine sodium and potassium during pulsatile and non-pulsatile hemodilutional cardiopulmonary bypass (abstract) 1980;59:526
Turner CJ, see Venkateswarlu T
Turner JM, see Campkin TV
Turner LA, Zuperku EJ, Purtock RV, Kampine JP. In vivo changes in canine ventricular conduction during halothane anesthesia 1980;59:327
Turner M, see Cowen MJ
Turner MS, see Ravindran RS
Turner PA, see Denson DD
Tweed A, see Biehl DR
Twersky RS, see Weinberg S
Tyberg JV, see Loarie DJ
  see Wilkinson PL
Tyce GM, see Rorie DK
Tyler DC, Cheney FW. Comparison of positive end-expiratory pressure and inspiratory positive pressure plateau in ventilation of rabbits with experimental pulmonary edema 1979;58:288
Tyler E, Caldwell C, Ghia JN. Transcutaneous electrical stimulation: an alternative approach to the management of postoperative pain 1982;61:449
Tyler IL. Control of pulmonary artery catheter pressures—an alternative (letter) 1984;63:467
  Hammill M. Gas analyzer or anesthesia circuit malfunction? Let room air decide (letter) 1984;63:702
  The relative pain inflicted by techniques used for insertion of needles (letter) 1984;63:373
Ueda I, Eyring H. Hydrogen ion concentration versus pH 1979;58:487
  Kamaya H. Molecular mechanisms of anesthesia 1984;63:929
  Oguchi K, Arakawa K. True oil/water partition coefficients of procaine and lidocaine and estimation of their dissociation constants in organic solvents 1982;61:56
  see Kamaya H
  see Yasubara H
Ullman JI, Stoelting RK. Internal jugular vein location with the ultrasound Doppler blood flow detector 1978;57:118
Ullyot DJ, see Wilkinson PL
Umlas J, Taff RH, Gauvin G, Swierk P. Anticoagulant monitoring and neutralization during open heart surgery—a rapid method for measuring heparin and calculating

Umlas J—*continued*
  safe reduced protamine doses 1983;62:1095
  Taff RH, Gauvin GP, Swierk P. More on protamine dosage (letter) 1984;63:784
Underwood P, Howland WS. Preoperative blood volume determination (questions and answers) 1976;55:275
Upton RA, Nguyen TL, Miller RD, Castagnoli N Jr. Renal and biliary elimination of vecuronium (ORG NC 45) and pancuronium in rats 1982;61:313
Urban BJ, McKain CW. Onset and progression of intravenous regional anesthesia with dilute lidocaine 1982;61:834
  see McKain CW
Urquilla PR, see Smith DJ
Ursillo RC, see Novack GD
Urzua J, Dominguez P, Quiroga M, Moran S, Irarrazaval M, Maturana G, Dubernet J. Preoperative estimation of risk in cardiac surgery 1981;60:625
  see Estafanous FG
  see Zurick AM
Usubiaga LE, see Aldrete JA
Utting JE, see Gray TC
Uy DS, see Anton AH
Uy NTL, see McKenzie R
v. Bormann B, Weidler B, Dennhardt R, Strum G, Scheld HH, Hempelmann G. Influence of epidural fentanyl on stress-induced elevation of plasma vasopressin (ADH) after surgery 1983;62:727
Vacanti CJ, Lynch TG. Hepatitis following enflurane (letter) 1980;59:890
Vagher P, see Epstein HM
Vakil AH, see Maliniak K
Valenta LJ, see Pulver JJ
Valeri CR. Blood components in the treatment of acute blood loss: use of freeze-preserved red cells, platelets, and plasma proteins 1975;54:01
Van Aken H, Puchstein C, Anger C, Heinecke A, Lawin P. Changes in intracranial pressure and compliance during adenosine triphosphate-induced hypotension in dogs 1984;63:381
Vandam LD. On the history of ideas in anaesthesia, Tenth Annual Becton, Dickinson and Company Oscar Schwidetzky Memorial Lecture (1976) 1976;55:467
  see Dripps RD
  To make the patient ready for anesthesia: medical care of the surgical patient (book review) 1981;60:171
  William T. G. Morton (letter) 1979;58:260
van der Aa J, see Berger JJ
  see Gravenstein N
van der Pol F, see Booij LHDJ
Vanderhoort JE, see Maze M
Vander Salm TJ. Atlas of bedside procedures (book review) 1980;59:228
van der Starre PJA, Scheijgrond HW, Reneman RS, Kolling JB. The use of ketanserin, a 5-hydroxytryptamine receptor antagonist, for treatment of postoperative hypertension following coronary artery bypass surgery 1983:62:63
van der Vusse GJ, Coumans WA, Kruger R, Verlaan C, Reneman RS. Effect of fentanyl on myocardial fatty acid and carbohydrate metabolism and oxygen utilization during experimental ischemia 1980;59:644
Van Dyke C, see Jatlow P
Van Dyke RA. A comparison of renal effects and metabolism of sevoflurane and methoxyflurane in enzyme-induced rats (guest discussion) 1975;54:835
  Hepatic centrilobular necrosis in rats after exposure to halothane, enflurane, or isoflurane 1982;61:812
  Hepatitis after use of two different fluorinated anesthetic agents (correspondence) 1975;54:125
  see Cohen EN
  see Gronert GA
  see Shingu K
  see Traynor CA
  Terminology and definition of word "metabolism" (questions and answers) 1976;55:760
Van Etten A, see Bloor BC
  see Fukunaga AF
Vanhoutte PM, see Shepherd JT
van Kleef D, see Moore DC
  see Nauta J
van Niekerk P, see Weis OF
Van Nyhuis LS, Miller RD, Fogdall RP. The interaction between *d*-tubocurarine, pancuronium, polymyxin B, and neostigmine on neuromuscular function 1976;55:224
van Poorten JF, Dhasmana KM, Kuypers RSM, Erdmann W. Verapamil and reversal of vecuronium neuromuscular blockade 1984;63:155
van Rensburg AJJ, see Mitchell G
Van Trigt P, see Christian CM
van Wezel HB, see Bovill JG
Varakian L, see Abboud TK
Varkey GP. Anesthetic considerations in the surgical repair of intracranial aneurysms (book review) 1982;61:890
Varma AB, see Howie MB
Varner PD, see McKay RD
Varonos D, see Kaniaris P
Vassallo HG, see Covino BG
Vatashsky E, Haskel Y, Aronson HB. Esophageal rupture and spinal anesthesia 1983;62:606
Vatner SF, see Priano LL
Vauclair R, see Hardy JF
Vaughan MS, Cork RC, Vaughan RW. Inaccuracy of liquid crystal thermometry to identify core temperature trends in postoperative adults 1982;61:284
  see Lees D
  Vaughan RW, Cork RC. Postoperative hypothermia in adults: relationship of age, anesthesia, and shivering to rewarming 1981;60:746
Vaughan RW, Bauer S, Wise L. Effect of position (semirecumbent versus supine) on postoperative oxygenation in markedly obese subjects 1976;55:41
  Bentley JB, Cork RC, Gandolfi AJ. Does evidence of reductive halothane biotransformation correlate with hepatic binding of metabolites in obese patients? (abstract) 1981;60:279
  Engelhardt RC, Wise L. Postoperative alveolar-arterial oxygen tension difference: its relation to the operative incision in obese patients 1975;54:433
  Miller MS, Gandolfi AJ, Bentley JB, Paplanus SH. Factors influencing enflurane disposition in the obese (abstract) 1980;59:562
  see Bentley JB
  see Borel JD
  see Calkins JM
  see Cobb ML
  see Cork RA
  see Cork RC
  see Lees D
  see Vaughan MS
  see Wilson SL
  Wilson SL, Waldbaum LS. Unrelenting hypotension associated with an acute abdomen in a comatose hemophiliac child: a case report 1976;55:346
Vega ET, see Pyles ST
Vegas O, Stoelting RK. Halothane MAC in dogs unchanged by phenobarbital 1976;55:677
Veith I, see Tan LT
Velazquez JL, Feingold A. Calibration of the Narokotest gas monitor for isoflurane (brief reports) 1976;55:441

  Feingold A, Walther P. Response time of the Narkotest anesthetic gas monitor 1977;56:395
Veloski J, see Seltzer JL
Vender JS, Epstein HM. Clifford C. Preadmission testing: it can make a difference! (abstract) 1982;61:219
  Watts DR. Differential diagnosis of hand ischemia in the presence of an arterial cannula 1982;61:465
Venkateswarlu T, Turner CJ, Carter JD et al. The tracheal bronchus: an unusual airway problem (brief reports) 1976;55:746
Ventafridda V, see Bonica JJ
Verlaan C, see van der Vusse GJ
Verma RS, Chatterji S, Mathur N. Diazepam and succinylcholine-induced muscle pains 1978;57:295
Vernon DD, Sarnaik AP. Extubation in epiglottitis (letter) 1984;63:469
Verosky M, see Bernstein KJ
  see Vulliemoz Y
  see Walter F
Via-Reque E, see Rattenborg CC
Viars P, see Benhamou D
  see Rouby JJ
Viby-Mogensen J, Hanel HK. Increased sensitivity to succinylcholine in a patient heterozygous for the silent and the fluoride-resistant gene 1978;57:422
  Pseudocholinesterase levels in pregnancy (letter) 1983;62:783
  see Sørensen O
Vickers MD. Medicine for anaesthetists (book review) 1978;57:156
  see Sykes MK
  Wood-Smith FG, Stewart HC. Drugs in anaesthetic practice (book review) 1979;58:163
Vicuna N, see Lalka D
Vidal-López F, Brachial plexus anesthesia using the omotrapezoid route 1977;56:486
Vidyasager D, see Braverman B
Viegas O. Correlation of plasma cholinesterase activity and duration of action of succinylcholine during pregnancy (guest discussion) 1977;56:81
  see Stoelting RK
  Stoelting RK. A question of statistics (correspondence) 1977;56:467
Viegas OJ, Cummins DF, Shumacker CA. Portable ventilation system for transport of critically ill patients 1981;60:760
  Ravindran RS, Shumacker CA. Gastric fluid pH in patients receiving sodium citrate 1981;60:521
  Ravindran RS, Stoops CA. Duration of action of sodium citrate as an antacid (letter) 1982;61:624
  Ravindran RS, Stoops CA. Duration of efficacy of sodium citrate as an antacid (abstract) 1982;61:220
  see Ravindran RS
Vieira E, Cleaton-Jones P, Austin JC, Moyes DG, Shaw R. Effects of low concentrations of nitrous oxide on rat fetuses 1980;59:175
Vieira ZEG, see Couto da Silva JMC
Viljoen JF. Propranolol and cardiac surgery: a problem for the anesthesiologist? (guest discussion) 1975;54:577
  see Estafanous FG
  see Joseph MM
  see Krantz EM
Villamater J, see Koren G
Villarreal-Guzman RA, see Toro-Matos A
Vinik HR, Reves JG, Wright D. Premedications with intramuscular midazolam: a prospective randomized double-blind controlled study 1982;61:933
  see Dundee JW
Virgilio RW, see Hobelmann CF Jr
  see Shackford SR
  see Sise MJ
Virtue RW. Comparison of gallamine with *d*-tubocurarine effects on fasciculations after succinylcholine 1975;54:81
  see Aldrete JA
Visconti JA, Tormo VJ, Dasta JF. Aminophylline–theophylline drug incompatibilities (letter) 1982;61:547
Vitek JJ, see Corssen G
Vitez TS, Difrancesco LV. Reversal of combination nondepolarized neuromuscular block 1983;62:1081
  Potency of metocurine during halothane $N_2O$ and $N_2O$–narcotic anesthesia 1978;57:116
  Soper LE, Soper PG. Chronic hypokalemia does not increase anesthetic dysrhythmias (abstract) 1982;61:221
Vlietstra RE, see Backer CL
Vogel A, see Bishop MJ
Volgyesi GA, see Jones PIE
  see Kolton M
von Colditz JH, see Palmer SK
Von der Lage FC Jr, see Ozdil T
Vongvises P, Panijayanond T. A parascalene technique of brachial plexus anesthesia 1979;58:267
VonLintel T, see Kim JM
Vourc'h G, Berretti E, Trichet B, Moncorge C, Camey M. Gas embolism associated with use of lasers for urethral surgery (letter) 1982;61:160
  see Tannieres ML
Vredevoe LA. New techniques for fiberoptic intubation and laryngeal examination (letter) 1981;60:617
Vree TB, Reekers-Ketting JJ, Fragen RJ, Arts THM. Placental transfer of midazolam and its metabolite 1-hydroxymethylmidazolam in the pregnant ewe 1984;63:31
Vries JK. Increased cerebrospinal fluid pressure during laryngoscopy and intubation for induction of anesthetics (guest discussion) 1975;54:690
Vucicevic D, see Cairoli VJ
Vucins EJ, Rusch JR, Grum CM. Vent stitch entrapment of Swan–Ganz catheters during cardiac surgery 1984;63:772
  see Kotrly KJ
Vuckovic DD, Rooney SM, Goldiner PL, O'Sullivan D. Aerosol anesthesia of the airway using a small disposable nebulizer 1980;59:803
Vulliemoz Y, see Bernstein KJ
  see Walter F
  Triner L, Verosky M, Hamm MW, Krishna G. Deuterated halothane—anesthetic potency, anticonvulsant activity, and effect on cerebellar cyclic guanosine 3′,5′-monophosphate 1984;63:495
Wade EJ, see Liu WS
Wade JG, see Biehl DR
  see Gregory GA
  Stevens WC. Isoflurane: an anesthetic for the eighties? 1981;60:666
Wadhwa RK, see Abouleish E
  see McKenzie R
Wagner DL, Moorthy SS, Stoelting RK. Administration of anticholinesterase drugs in the presence of beta-adrenergic blockade 1982;61:153
Wahba WM. Analysis of ventilatory depression by enflurane during clinical anesthesia 1980;59:103
  Influence of aging on lung function—clinical significance of changes from age twenty 1983;62:764
Wahle WM, see Link WJ
Wajskol A, see McCullough LS
  see Nigrovic V
Wakid N, see Baraka A
Walajahi FW, Karasic LH. Anesthetic management of a patient with dystonia musculorum deformans 1984;63:616
Wald A. Discoloration of enflurane (letter) 1981;60:843
  Neidzwski JY. Front panel cover for Frazer–Harlake ventilator (letter) 1983;62:619
  Switchover valve failure (letter) 1981;60:843
Waldbaum LS, see Owens WD
  see Vaughan RW

Waldenström A, see Pontén J
Waldman J, Kaufer H, Hensinger RN, Callaghan ML, Lieding KG. Wake-up technic to avoid neurologic sequelae during Harrington rod procedure: a case report 1977;56:733
  see Radtke N
Walker DR, see Lell WA
Walker JS, Shanks CA, Brown KF. Determinants of *d*-tubocurarine plasma protein binding in health and disease 1983;62:870
Wall J, see Alexander JJ
Wallace CT, see Hood JB
Wallace G, Mindlin LJ. A controlled double-blind comparison of intramuscular lorazepam and hydroxyzine as surgical premedicants 1984;63:571
Wallace R, see Kareti RKP
Waller JL, Hug CC Jr, Nagle DM, Craver JM. Fentanyl/oxygen "anesthesia" and coronary bypass surgery (abstract) 1980;59:562
  Johnson SP, Kaplan JA. Usefulness of pulmonary artery catheters during aortocoronary bypass surgery (abstract) 1982;61:221
  Kaplan JA, Bauman DI, Craver JM. Clinical evaluation of a new fiberoptic catheter oximeter during cardiac surgery 1982;61:676
  Kaplan JA, King SB, Douglas JS, Craver JM. Percutaneous transluminal coronary angioplasty: anesthesiologist's role (abstract) 1981;60:280
  see Lonergan JG
  Zaidan JR, Kaplan JA, Bozeman R. Hemodynamic responses to vascular cannulation before coronary bypass surgery (abstract) 1980;59:563
Wallin RF, Regan BM, Napoli MD et al. Sevoflurane: a new inhalational anesthetic agent 1975;54:758
  Thermoregulatory defect in rats during anesthesia (guest discussion) 1977;56:14
Walson PD. Pain control in parturition (correspondence) 1977;56:598
  see Salts L
Waltemath CL, Erbguth PH. An inexpensive blood warmer (brief reports) 1975;54:155, (correspondence) 1975;54:816
Walter CW. Use of electrocautery during operation following ether skin prep (questions and answers) 1975;54:210
Walter F, Vulliemoz Y, Verosky M, Triner L. Effects of halothane on the cyclic 3′,5′-adenosine monophosphate enzyme system in human platelets 1980;59:856
Walther P, see Velazquez JL
Walton B, Simpson R
  Hepatitis after use of two different fluorinated anesthetic agents (correspondence) 1975;54:125
Walton JR, see Shapiro BA
Walts LF. Effects of neostigmine on intestine (questions and answers) 1977;56:596
  Rusin WD. The influence of succinylcholine on the duration of pancuronium neuromuscular blockade 1977;56:22
  see Saucier N
Wang BC, Hillman DE, Spielholz NI, Turndorf H. Chronic neurological deficits and nesacaine-CE—an effect of the anesthetic, 2-chloroprocaine, or the antioxidant, sodium bisulfite? 1984;63:445
Wang JF. Fiberoptic laryngoscope guide and protector 1977;56:126
Wang Y, see Rosenblatt RM
Wanna HT, Gergis SD. Procaine, lidocaine, and ketamine inhibit histamine-induced contracture of guinea pig tracheal muscle in vitro 1978;57:25
Wansbrough SR, see Rees DI
Wapner S, see Conner JT
Warber RRF, see Miller R
Ward AM, see Watkins J
Ward CF, Gagnon RL, Benumof JL. Wheezing after induction of general anesthesia: negative expiratory pressure revisited 1979;58:49
  Gamel DM, Benumof JL. Endotracheal tube cuff herniation: a cause of delayed airway obstruction 1978;57:114
  Kemp J. A CAT with a birth defect (letter) 1984;63:701
  Ozaki G. Adaptation of Doppler binaural headset for use with a personalized earpiece (correspondence) 1977;56:469
  Reisner LS, Zlott LS. Murphy's law and humidification (letter) 1983;62:460
Ward DS, Bellville JW. Reduction of hypoxic ventilatory drive by dopamine 1982;61:333
  Stimulation of hypoxic ventilatory drive by droperidol 1984;63:106
Ward EM, Rorie DK, Nauss LA, Bahn RC. The celiac ganglia in man: normal anatomic variations 1979;58:461
Wark JA, see Rocco AG
Warner EJ, see Warner LO
Warner LO, Beach TP, Garvin JP, Warner EJ. Halothane and children: the first quarter century 1984;63:838
Warner MA, Hughes DR, Messick JM. Anesthetic management of a patient with pulseless disease 1983;62:532
  Hughes DR, Messick JM. On unusual values of PAD and PAOP (letter) 1984;63:89
Warpinski MA, see Reitan JA
Warren CH Jr, see Moorthy SS
Warren FZ. Handbook of medical acupuncture (book review) 1977;56:171
Warren JE, Morrow DH. Antiarrhythmic anesthetic action. II. The effect of methoxyflurane on ventricular automaticity 1977;56:194
Warren PJ, see Bovill JG
Warren TM, Datta S, Ostheimer GW. Lumbar epidural anesthesia in patients with multiple sclerosis (letter) 1983;62:856
  Datta S. Ostheimer GW. Lumber epidural anesthesia in a patient with multiple sclerosis 1982;61:1022
  Datta S, Ostheimer GW, Naulty JS, Weiss JB, Morrison JA. Comparison of the maternal and neonatal effects of halothane, enflurane, and isoflurane for cesarean delivery 1983;62:516
Warshaw J, see Kwon P
Washington E, see Samuels SI
Waskell L, Gonzales J. Dependence of microsomal methoxyflurane O-Demethylation on cytochrome P-450 reductase and the stoichiometry of fluoride ion and formaldehyde release 1982;61:609
  see Koblin DD
Wassill VM, Hill GE, Jacoby RM. Antagonism of the cardiovascular depressant effects of protamine by calcium (abstract) 1980;59:564
Watanabe H, see Hashimoto Y
Watchmaker G, see Wyrobek AJ
Waterhouse M. Practical mathematics in allied health (book review) 1980;59:637
Waterman PM, Albin MS, Smith RB. Malignant hyperthermia (case report) 1980;59:220
  see Freilich JD
  Smith RB. Tobramycin–curare interaction 1977;56:587
Waters J, see Schoeppel SL
Waterson CK, Calkins JM, Quan SF, Otto CW, Hameroff SR. High-frequency jet ventilation operational guidelines (abstract) 1982;61:222
  see Calkins JM
  see Hameroff SR
  see Otto CW
Watkins FC. Terminology in anesthesia (questions and answers) 1975;54:640
Watkins J, Ward AM. Adverse response to intravenous drugs (book review)

1979;58:162
Watkins ML, see Buzello W
Watson CB. Colloid or crystalloid? (letter) 1981;60:228
  see Mackie AM
Watson J, Moore A, McQuay H, Teddy P, Baldwin D, Allen M, Bullingham R. Plasma morphine concentrations and analgesic effects of lumbar extradural morphine and heroin 1984;63:629
Watson JE, see Koblin DD
Watson RL, see Moore WE
  see Muldoon S
  see Rayburn RL
Watson TD, see Raj PP
Watt RC, see Hameroff SR
Watters C, see Ford DJ
Watts DR, see Vender JS
Wattwil LM, see Malina JR
Wattwil M, see Rawal N
Waud BE, Farrell L, Waud DR. Lithium and neuromuscular transmission 1982;61:399
  see Farrell L
  see Welch GW
  Waud DR. Temperature and the potency of relaxants (letter) 1981;60:455
Waud DR, see Farrell L
  see Waud BE
Wauquier A, see Sebel PS
Waxman K, Shoemaker WC, Lippmann M. Cardiovascular effects of anesthetic induction with ketamine 1980;59:355
Way WL, Hosobuchi Y, Eger EI II, Johnson BH. Anesthesia does not increase cerebrospinal fluid opioid peptides in humans (abstract) 1982;61:223
  see Johnston RR
Weaver JM, see Rosenblatt RM
Webb J, see Bishay EG
Weber DM, see Hagan CH
Weber L, Hirshman CA. Cimeditine for prophylaxis of aspiration pneumonitis: comparision of intramuscular and oral dosage schedules 1979;58:426
Weber RJ, see Dasta JF
Weber TR, see Rao CC
Webster LR, see Kawamura R
  see Lunn JK
  see Wong KC
  Stanley TH. Anesthetic requirements and cardiovascular effects of fentanyl-oxygen and fentanyl-diazepam-oxygen anesthesia in man 1978;57:411
Wedel DH, see Cucchiara RF
Weeks DB, Comer PB. A PEEP device for anesthesia circuits 1977;56:578
  Micronebulizer for anesthesia circuits (letter) 1981;60:537
  PEEP measurement (correspondence) 1978;57:144
  Ramsey FM. Laboratory investigation of six artificial noses for use during endotracheal anesthesia 1983;62:758
  see Clark CC
Weidler B, see v. Bormann B
Weil MH, Henning JR. New concepts in the diagnosis and fluid treatment of circulatory shock, Thirteenth Annual Becton, Dickinson and Company Oscar Schwidetzky Memorial Lecture 1979;58:124
Weinberg S, Nakajo M, Rao M. Airway management in children with bacterial tracheitis 1984;63:860
  see Fyman PN
  Twersky RS. Neuroleptic malignant syndrome 1983;62:848
Weinreich A, see Eisele V
Weinreich AI, see Girnar DS
Weintraub HD, see Lee DS
Weintraub M, see Weis OF
Weintraub WH, see Coran AG
Weir L, see McQuay H
Weis FR Jr, see Schuder RJ
Weis OF, Müller FO, Lyell H, Badenhorst CH, van Niekerk P. Materno–fetal cholinesterase inhibitor poisoning 1983;62:233
  see Meyer BH
  see Müller FO
  Sriwatanakul K, Alloza JL, Weintraub M, Lasagna L. Attitudes of patients, housestaff, and nurses toward postoperative analgesic care 1983;62:70
Weisfeldt ML, see Rogers MC
Weiskopf RB, Bogetz MS. Minimum alveolar concentrations (MAC) of halothane and nitrous oxide in swine 1984;63:529
  Townsley MI, Riordan KK, Chadwick K, Baysinger M, Mahoney E. Comparison of cardiopulmonary responses to graded hemorrhage during enflurane, halothane, isoflurane, and ketamine anesthesia 1981;60:481
Weiss DL, see Dorris GG
Weiss JB. Methoxyflurane and trichlorothylene self-administered by parturients, medical and legal aspects (questions and answers) 1977;56:322
  see Datta S
  see Warren TM
Weiss JL, see Cork RC
Weiss R, Halevy S, Almonte RO, Gundersen, Hinsvark ON, O'Brien JE. Comparison of lidocaine and 2-chloroprocaine in paracervical block: clinical effects and drug concentrations in mother and child 1983;62:168
Weiss RR, Nathanson HG, Tehrani MR, Tejani NA, Halevy S, Mann LI. Paracervical block with 2-chloroprocaine 1977;56:709
Weissman DB, Ehrenwerth J. Prolonged neuromuscular blockade in a parturient associated with succinylcholine 1983;62:444
  Ehrenwerth J. Succinylcholine in obstetrics (letter) 1983;62:1051
Weitzner SW, see Karis JH
Welch GW, Feldman HS. Intravenous nalbuphine (letter) 1981;60:168
  Waud BE. Effect of bretylium on neuromuscular transmission 1982;61:442
Welch MH, see Guenter CA
Welch WD, see Eyler SW
Weldon OGW, see Bastard OG
Weldon S, see Gandolfi AJ
Weldon ST, see Blitt CD
Wellons HA Jr, see Lake CL
Wells PH, see Kaplan JA
Welman S, see Brock-Utne JG
Welter LO, see Knight PR
Welti RS, Moldenhauer CC, Hug CC Jr, Kaplan JA, Holbrook GW. High-dose hydromorphine (Dilaudid) for coronary artery bypass surgery 1984;63:55
Wender RH, see Conner JT
Weng JT, see Gooding JM
  see Subaiya L
  see Youngberg JA
Wenig BL, see Neuman GG
Weniger FC, see Domaoal AM
Wesseling H, see Sia RL
West JB. New advances in pulmonary gas exchange, Tenth Annual Becton, Dickinson, and Company Oscar Schwidetzky Memorial Lecture 1975;54:409
Westengard JC, see Moorehead MT
Westenskow DR, Jordan WS, Jordan R, Gillmor ST. Evaluation of oxygen monitors for use during anesthesia 1981;60:53
  Jordan WS, Hayes JK. Feedback control of enflurane delivery in dogs—inspired compared to end-tidal control 1983;62:836
  Jordon WS, Hodges MR, Stanley TH. Correlation of oxygen uptake and cardiovascular dynamics during $N_2O$-fentanyl and $N_2O$-thiopental anesthesia in the dog 1978;57:37
  Jordon WS, Pace NL. Intraoperative monitoring of arterial $P_{CO_2}$: comparing end-tidal and transcutaneous sensors (abstract) 1982;61:223
  Meline LJ, Pace NL, Bodily MN.

Westenshow DR—*continued*
  Meline LJ—*continued*
    Sodium nitroprusside induced hypotension with computer adjustment for varying drug sensitivity (abstract) 1984;63:281
  see Bailey PL
  see Pace NL
  Wong KC, Johnson CC, Wilde CS. Physiologic effects of deep hypothermia and microwave rewarming: possible application for neonatal cardiac surgery 1979;58:297
  Wong KC. Microwave rewarming (letter) 1980;59:161
Westman HR. Medical examination review, vol. 12, anesthesiology, 6th edition (book review) 1984;63:705
  Pain management (book review) 1984;63:705
  Recovery room care (book review) 1984;63:172
  see Cook DR
Westover CJ Jr, see Smith NT
Westra P, see Sia RL
Wetstone DL, see Hornbein TF
  see Wong KC
Wexler DB, see Grundy BL
Wexler HR, see Kenefick JP
  see Lampe KM
Wexler L, see Smith NT
Weymuller EA Jr, see Bishop MJ
  see Wynands JE
Whalley DG, see Lieberman RW
  see Quintin L
  see Ralley FE
  see Sprigge JS
  see Wynands JE
Whang-Peng J, see Lees DE
Wharton RS, Sievenpiper TS, Mazze RI. Developmental toxicity of methoxyflurane in mice 1980;59:421
  Wheeler AS, Patel KF, Spain J. Pulmonary edema during beta-2-tocolytic therapy (letter) 1981;60:695
  see James FM
  see Meguiar RV
Whickham BL, see Noe FE
Whisler WW, see Ford EW
Whitcher C, Piziali RL. Monitoring occupational exposure to inhalation anesthetics 1977;56:778
Whitcher CE, see Brodsky JB
White A, see Lawson NW
  see Loarie DJ
White AE, see Eger EI II
  see Wilkinson PL
  Stevens WC, Eger EI II, Mazze RI, Hitt BA. Enflurane and methoxyflurane metabolism at anesthetic and at subanesthetic concentrations 1979;58:221
White D, see Gattinoni L
White E, see Schuder RJ
White JF, see James MFM
White PF. Continuous infusions of thiopental, methohexital or etomidate as adjuvants to nitrous oxide for outpatient anesthesia (abstract) 1984;63:282
  see Johnston RR
White RD. Drugs in cardiac supportive care 1976;55:633
  see Mallow JE
White S, see McGarrigle R
Whitesell RC, Asiddao C, Gollman D, Jablonski J. Relationship between arterial and peak expired carbon dioxide pressure during anesthesia and factors influencing the difference 1981;60:508
  see Asiddao CB
Whittle B, see Harcus AW
Whitty AJ, see Noe FE
Whitwam JG, see Lumley J
Widdicombe JG, Respiratory physiology, vol II (book review) 1978;57:384
Widman B, see Rawal N
Widmer S, see Schwartz AJ
Wiener EL, see Kennedy PJ
Wightman AE, see Malloy WF
Wilbrink J, see Andriano KP
Wilcox BR, see Brown DR
Wilcox JR, see Kallus FT
Wilde CS, see Westenskow DR
Wildsmith JAW, Brown DT. Isobaric spinal anesthesia (letter) 1982;61:714
Wilkinson C, see Schoeppel SL
Wilkinson CJ, Ham J, Miller RD. Clinical anesthesia (book review) 1980;59:638
  Sanders JH. Massive doses of nitroglycerin in a patient with variant angina 1980;59:707
Wilkinson PL, Graham BH, Moyers JR, Hamilton WK, Ports TA, Ullyot DJ, Chatterjee K. Changes in mixed venous and coronary sinus $P_{50}$ secondary to anesthesia and cardiac disease 1980;59:751
  see Bennett MJ
  see Loarie DJ
  Tyberg JV, Moyers JR. Rate pressure product correlates with myocardial oxygen consumption during anesthesia (abstract) 1980;59:564
  Tyberg JV, Moyers JR, White AE. Correlates of myocardial oxygen consumption when afterload changes during halothane anesthesia in dogs 1980;59:233
Wilks DH. Advances in anesthesia, volume 1 (book review) 1984;63:1144
  see Gharooni S
Willenkin E, see Sivarajan M
Williams A see Belani KG
Williams CH, see Buzello W
Williams GD, see Flacke JW
Williams JE, see Jones RM
  see Khalil SN
Williams RT, Maltby JR. Airway intubator (letter) 1982;61:309
  see Palazzo M
Williams TJ, see Lough MD
Williams V, see Downing JW
Williamson DC III, Munson ES. Correlation of peripheral venous and arterial blood gas values during general anesthesia 1982;61:950
Williams-Van Alstyne SI, see Blitt CD
Willner J. Phosphorylase activity and malignant hyperthermia (letter) 1984;63:88
Wilson AI, see Mazze RI
Wilson C, see Horrigan RW
  see Johnston RR
Wilson F, Park WG. Basic resuscitation and primary care (book review) 1981;60:458
Wilson NE, see Brand JB
Wilson R, see Aldrete JA
Wilson RD. Balanced anesthesia (questions and answers) 1976;55:907
Wilson RS, see Fuleihan SF
Wilson SL, Mantena NR, Halverson JD. Effects of atropine, glycopyrrolate, and cimetidine on gastric secretions in morbidly obese patients 1981;60:37
  Miller RN, Wright C et al. Prolonged neuromuscular blockade associated with trimethaphan: a case report 1976;55:353
  see Meyers EF
  see Vaughan RW
  Vaughan RW, Stephen CR. Awareness, dreams, and hallucinations associated with general anesthesia 1975;54:609
Wingard DW. A stressful situation 1980;59:321
  Bobko S. Failure of lidocaine to trigger porcine malignant hyperthermia 1979;58:99
  see Larson GF
  see Peters KR
Wingard LB Jr. Basic and clinical pharmacology (book review) 1983;62:784
Winn R, see Burney RG
Winnie A. Correction (letter) 1980;59:460
  see Baraka A
Winnie AP. Gastric acidity and glycopyrrolate premedication (letter) 1979;58:157
  Radonjic R, Akkineni SR, Durrani Z. Factors influencing distribution of local anesthetic injected into the brachial plexus sheath 1979;58:225
  Ramamurthy S, Durrani Z et al. Interscalene cervical plexus block: a single-injection technic 1975;54:370
  see Baraka A
  see Edwards R

  see Grundy EM
  see Ramamurthy S
  Tay CH, Patel KP, Ramamurthy S, Durrani Z. Pharmacokinetics of local anesthetics during plexus blocks 1977;56:852
Winning TJ, Brock-Utne JG, Downing JW. Nausea and vomiting after anesthesia and minor surgery 1977;56:674
Winrow MJ. Hepatitis after use of two different fluorinated anesthetic agents (correspondence) 1975;54:125
Winter J, see Ferrer-Brechner T
Winter P, see Sivarajan M
Winter PM, see Cook TL
  see Harper MH
  see Hornbein TF
  see Smith RA
Winters WD. Ketamine and epilepsy (correspondence) 1976;55:449
Wirdzek PR, see Dionne RA
  see Gelfman SS
Wirta MG, see Burkett L
Wise L, see Vaughan RW
Witcher T, see Galindo A
Witt WO, see Aldrete JA
Woelfel SK, see Brandom BW
  see Cook DR
  Techniques of blood transfusion (book review) 1984;63:628
Wolf S, see Sprague DH
Wolfe T, see Haselby KA
Wolfe TM, see Dierdorf SF
  see Roesch C
Wolfson B, Freed B. Influence of alcohol on anesthetic requirements and acute toxicity 1980;59:826
  see Cook DR
  see Cottrell JE
  see Domaoal AM
Woliner M, see Steffey EP
Wollack AR, see Pan TH
Wollman SB, Kushins LG. Survival following massive pulmonary hemorrhage complicating pulmonary embolectomy: a case report 1976;55:182
  see Kopman AF
Womble J, see Hameroff SR
Wong AL, Brodsky JB. Asystole in an adult after a single dose of succinylcholine 1978;57:135
  see Brodsky JB
Wong KC. Narcotics are not expected to produce unconsciousness and amnesia (editorial) 1983;62:625
  Ohmura A, Roberts TH, Webster LR, Cook GL. Anesthetic management for separation of craniopagus twins 1980;59:883
  Peter JL, Roberts TS, McRea JC, Fukumasu H. Lack of CNS depression from large doses of trimethaphan in sheep 1977;56:06
  see Hill GE
  see Kawamura R
  see Liu WS
  see Pace NL
  see Westenskow DR
  Sullivan S, Wetstone DL. Antagonistic effect of morphine on the positive inotropic response of ouabain on the isolated rabbit heart 1975;54:787
  The role of profound hypothermia in infants undergoing surgical correction of complicated heart defects (guest discussion) 1975;54:626
Wong P, see Wynands JE
  Whalley DG, Sprigge JS, Townsend GE, Patel YC. Oxygen-fentanyl anesthesia in patients with poor left ventricular function: hemodynamics and plasma fentanyl concentrations 1983;62:476
Woo J, see Morison DH
Woo SW. Ambulatory anesthesia care, International Anesthesiology Clinics, volume 20 (book review) 1982;61:807
Wood AJ, see Wood M
Wood DD, see Chu LSW
Wood DW. Adult respiratory distress syndrome and pancuronium bromide (correspondence) 1975;54:620
Wood M, Stone WJ, Wood AJ. Plasma binding of pancuronium: effects of age, sex, and disease 1983;62:29
  Wood AJJ. Contrasting effects of halothane, isoflurane, and enflurane on in vivo drug metabolism in the rat 1984;63:709
Woodcome HA, see Snow JC
Woodham B, see Paul WL
Woodruff LF, see Boehm FH
Woodruff RE, see Mazze RI
Woods EF, see Martis L
Woods M, see Young AE
Woods S, see Downing JW
Woodside JR Jr, Beckman JJ, Althaus JS, Miller ED Jr. Central depletion of catecholamines—importance of hypertension and anesthesia 1984;63:482
Wood-Smith FG, see Vickers MD
Woodward A, see Lunn JK
Woolf CR. The clinical core of respiratory medicine (book review) 1982;61:1027
Woolfe WA, see Craft JB Jr
Wootton DG, see Katz H
Wortham BG, see Rubin AS
Wright BD, see Bennett R
  see Debrand M
  see Dubick MN
  see Huang KC
  see Lee TS
  see Tsueda K
Wright BJ, see Blitt CD
Wright C, see Wilson SL
Wright CB, see Pochanapring A
Wright D, see Vinik HR
Wright FG Jr, Foley MF, Downs JB et al. Hypoxemia and hypocarbia following intermittent positive-pressure breathing 1976;55:555
Wright JP. Anesthetic considerations in preeclampsia—eclampsia 1983;62:590
Wright PL, see Hanson GC
Wright R, see Eisele JH
Wright RG, see Abboud TK
  see Rolbin SH
Wright WA, see Blitt CD
Wright WW. USP oxygen standards (letter) 1980;59:314
Wu LS, see Dasta JF
Wu ML, see Brodsky JB
Wu WH, see Ohn KC
Wurzel HA, see Aukburg SJ
Wyant GM. Mechanical misadventures in anesthesia (book review) 1979;58:262
Wylie EJ, see Roizen MF
Wyman MG, see McNamara PJ
Wymore ML, see Reitan JA
Wynands JE. Anesthesia for patients with heart block and artificial cardiac pacemakers 1976;55:626
  Emergency operation during acute myocardial infarction (case history discussion) 1975;54:268
  Left heart assist device: early clinical experiences with management of postperfusion low cardiac output (guest discussion) 1977;56:407
  see Quintin L
  see Ralley FE
  see Sprigge JS
  Townsend GE, Wong P, Whalley DG, Srikant CB, Patel YC. Blood pressure response and plasma fentanyl concentrations during high- and very high-dose fentanyl anesthesia for coronary artery surgery 1983;62:661
  Wong P, Townsend GE, Sprigge JS, Whalley DG. Narcotic requirements for intravenous anesthesia 1984;63:101
Wynder J, Brodsky JB, Merrell RC. Massive obesity and arterial oxygenation 1981;60:691
Wyrobek AJ, Brodsky JB, Moore D, Watchmaker G, Cohen EN. Sperm studies in anesthesiologists (abstract) 1981;60:281
Yacoub M, see Hupert C
Yagiela JA, Benoit PW, Buoncristiani RD, Peters MP, Fort NF. Comparison of myotoxic effects of lidocaine with epinephrine in rats and humans 1981;60:471

Yakaitis RW, Thomas JD, Mahaffey JE. Effects of intraoperative PEEP on postoperative arterial oxygenation 1975;54:427
Yamada T, see Ghoneim MM
Yamamura T, Fukuda M, Takeya H, Goto Y, Furukawa K. Fast oscillatory EEG activity induced by analgesic concentrations of nitrous oxide in man 1981;60:283
  Kimura T, Furukawa K. Effects of anesthetics on central vagal tone (letter) 1984;63:371
  Kimura T, Furukawa K. Effects of halothane, thiamylal, and ketamine on central sympathetic and vagal tone 1983;62:129
  see Kinoshita O
  see Mishima S
Yamashiro SM, see Grodins FS
Yamashita S, see Kinoshita O
Yanagi T, see Abboud TK
Yanagida H, Corssen G, Ceballos R, Strong E. Alcohol-induced pituitary adenolysis: how does it control intractable cancer pain?—An experimental study using tooth pulp-evoked potentials in rhesus monkeys 1979;58:279
  Kemi C, Suwa K. The effects of stellate ganglion block on the idiopathic prolongation of the Q-T interval with cardiac arrhythmia (The Romano-Ward syndrome) 1976;55:782
Yang E, Lee C, Tran B. Optimum dose of edrophonium for reversal of atracurium neuromuscular block (abstract) 1984;63:283 Yawn D
  see Saleh-Shenaq S
  see Lee C
  see Lippmann M
Yang JC, Clark WC, Dooley JC, Mignogna FV. Effect of intranasal cocaine on experimental pain in man 1982;61:358
Yarbrough JW, see Chapin JW
Yared JP, see Baraka A
  see Zurick AM
Yasubara H, Sakamoto K, Ueda I. Dissociation between local anesthetic and membrane-stabilizing actions in antiarrhythmic beta-adrenergic blockers and local anesthetics 1981;60:897
Yeakel AE, see Lee CM
Yeh SDJ, see Chu LSW
Yeh SU, see Abboud TK
Yelich SJ, see Ovassapian A
Yhap EQ, see Hicks HC
Yoachim J, see Shapiro HM
Yoder RD. Liquid crystal thermometry (letter) 1979;58:351
Yonejura ML, see Craft JB
Yonemura K, see Juang MS
Yonetani D see Loeser EA
Yoon HJ, see Smith DJ
Yost LC, Bernhard WN, Merrill C, Turndorf H. Oxygen-air blending nomogram 1977;56:290
  see Bernhard WN
Young AE, Fencl V, Woods M, Dmochowski J, Couch NP. Cerebral surface pH changes during asphyxia, hypotension, and circulatory arrest in the dog 1977;56:817
Young DS, see Brown SS
Young HF, see Schettini A
Young P, see Diamant M
Young SR. Methoxyflurane and trichloroethylene self-administered by parturients, medicolegal aspects (questions and answers) 1977;56:323
  Stoelting RK, Bond VK et al. Methoxyflurane biotransformation and renal function following methoxyflurane administration for vaginal delivery or cesarean section 1976;55:415
Youngberg JA. Gas embolism during encephalography (case history comment) 1976;55:144
  Mechanical ventilation with a non-rebreathing system to produce hypocarbia in children (abstract) 1980;59:565
  Subaiya C, Graybar GB, Weng JT, Adler E, Texidor M. Alfentanil for day-stay surgery in children: an evaluation (abstract) 1984;63:284
Yukioka H, see Tatekawa S
  Tatekawa S, Nishimura K, Fujimori M. A study of a noninvasive method for measuring central venous pressure during general anesthesia 1981;60:901
Zaccari J, see Graham CW
  see Tremper KK
Zahed B, Miletich DJ, Ivankovich AD, Albrecht RF, Toyooka ET. Arrhythmic doses of epinephrine and dopamine during halothane, enflurane, methoxyflurane, and fluroxene anesthesia in goats 1977;56:207
Zaidan JR, Philbin DM, Antonio R, Savarese J. Hemodynamic effects of metocurine in patients with coronary artery disease receiving propranolol 1977;56:255
  see Kates RA
  see Lonergan JG
  see Waller JL
Zaiss C, see Bodai BI
Zamora AM, see Grundy EM
Zandstra DF, see Sia RL
Zarday Z, see Forbat AF
Zaret B, see Barash PG
Zaritsky A, see Chernow B
Zarmakoupis PK, see Apostolou GA
Zarzur E. Anatomic studies of the human lumbar ligamentum flavum 1984;63:499
Zauder HI, see Stehling LC
Zauder HL. Anesthesia for orthopaedic surgery (book review) 1980;59:813
  see Jones DJ
  see Patil VU
Zebrowski ME, Gutsche BB. More on intravascular migration of an epidural catheter (letter) 1979;58:531
Zegveld C, Knape H, Smits J, Belopavlovic M, Caron D, Gallant J, Stockman A, Boghaert A. Domperidone in the treatment of postoperative vomiting: a double-blind multicenter study 1978;57:700
Zeh DW, Katz RL. New nerve stimulator for monitoring neuromuscular blockade and performing nerve blocks 1978;57:13
Zeitlin GL, see Owens WD
Zeligs MA, Lockhart CH. Perioperative hypoglycemia in a child treated with propranolol 1983;62:1035
Zeok SS, see Tsueda K
  Teusda K. Failure of a cephalothin test dose to produce anaphylaxis (letter) 1980;59:393
Zetner JL. The heroin solution (book review) 1983;62:959
Zikria BA, see Stanley TH
Ziment I. Respiratory pharmacology, and therapeutics (book review) 1979;58:447
Zimmer M, see Lanz E
Zimmerman BL. Arrhythmogenicity of theophylline and halothane used in combination (letter) 1979;58:259
Zlott LS, see Ward CF
Zorab JSM, Baskett PJF. Immediate care (book review) 1978;57:517
Zsigmond EK, Matsuki A, Kothary SP et al. Arterial hypoxemia caused by intravenous ketamine 1976;55:311
  see Covino BG
  see Domino EF
Zuckerman L, see Epstein HM
Zuperku EJ, see Turner LA
Zurick AM, see Estafanous FG
  Urzua J, Yared JP, Estafanous FG. Comparison of hemodynamic and hormonal effects of large single-dose fentanyl anesthesia and halothane/nitrous oxide anesthesia for coronary artery surgery 1982;61:521
Zwagil LW, Jarboe TM. Cardiopulmonary effects of PEEP and CPAP (special correspondence) 1978;57:346
Zwanikken P, see Andriano KP

Anesthesia
and Analgesia

# Subject Index

# Ten-Year Cumulative Index
# 1975–1984

Journal of the International Anesthesia Research Society

# Subject Index

- **Abducens nerve,** see Eye
- **Abortion,** see Pregnancy
- **Acetate,** see Metabolism
- **Acetazolamine,** see Carbon dioxide
- **Acetylcholine**
  - brain, reduction of enflurane-induced spike activity by scopolamine 1980;59:417
- **Acid-base equilibrium**
  - acidosis, metabolic, detection and differentiation in parturients 1980;59:929
  - alkalosis
    - effects on electrically stimulated atrial arrhythmias in digitalized dogs 1981;60:302
    - respiratory, acute hypocapneic hypokalemia 1977;56:786
    - respiratory, pentobarbital-halothane effects 1980;59:839
    - respiratory vecuronium recovery and hypocarbia 1984;63:608
    - treatment by acetazolamide 1981;60:608
  - anesthesia and hemorrhage 1981;60:481
  - bicarbonate, sodium, comparison with THAM in heart resuscitation after ventricular fibrillation in dogs 1977;56:38
  - calculation and correction of variables with a versatile computer program 1981;60:889
  - computer programs (letter) 1982;61:475
  - detection and differentiation in parturients (abstract) 1980;59:551
  - electrolyte disorders, carbon dioxide titration 1975;54:299
  - metabolic, treatment of alkalosis with acetazolamide 1981;60:608
  - neonatal
    - epidural anesthesia for cesarean section in diabetic parturients 1981;60:574
    - spinal anesthesia in diabetic parturients 1982;61:662
  - pH
    - calculation of mean pH values (letter) 1979;58:63
    - central tendency and the meaning of mean for pH values 1979;58:1
    - cerebral surface, changes during asphyxia, hypotension, and circulatory arrest in dog 1977;56:817
    - cerebrospinal fluid, effect on spinal anesthesia 1975;54:455
    - dependence of narcotics and narcotic antagonists in clinical anesthesia 1976;55:253
    - effect of cimetidine 1979;58:183
    - effects on protein binding of lidocaine 1978;57:478
    - gastric, neonatal 1978;57:98
    - hydrogen ion concentration versus 1979;58:487
    - interpretation of data (correspondence) 1978;57:379
    - statistical analysis of data (correspondence) 1978;57:143
  - respiratory, effects of hypocapnia on electrically stimulated atrial arrhythmias in digitalized dogs 1981;60:302
  - THAM, comparison with sodium bicarbonate in heart resuscitation after ventricular fibrillation in dogs 1977;56:38
  - theoretic significance of pH dependence of narcotics and narcotic antagonists 1976;55:253
  - thoracoabdominal aortic aneurysms, resection of (abstract) 1982;61:213
- **Acidosis,** see Acid-base equilibrium
- **Acromegaly**
  - laryngeal stenosis 1976;55:57
- **Acupuncture**
  - analgesia, neurobiologic research 1983;62:335
  - analgesic effects (abstract) 1983;62:280
  - anesthesia, a clinical study 1976;55:508
  - comparison with codeine on postoperative dental pain 1977;56:473
  - constitutes practice of medicine 1977;56:154
  - incidence of prolonged pain relief 1976;55:229
  - obstetrics 1975;54:83
  - varied stimulation intensity 1982;61:499
- **Addiction,** see Analgesics, abuse
- **Adenosine triphosphate,** see
  - Anesthetic techniques, hypotensive
  - Metabolism
- **Adenotonsillectomy,** see Surgery
- **Adenylate cyclase,** see Enzymes
- **Adiposis dolorosa**
  - management of intractable pain with intravenous lidocaine 1976;55:257
- **Adrenal,** see
  - Hormones, adrenocorticotropic, aldosterone, corticosteroid
  - Surgery, adrenalectomy, pheochromocytoma

  - catecholamines
- **Adrenergic,** see
  - Receptors
  - Sympathetic nervous system
- **Age factors**
  - (abstract) 1984;63:184, 197
  - anesthetic potency, cyclopropane used to test anesthetic requirement in the elderly 1984;63:998
  - arrhythmia, following reversal of neuromuscular blocking agents in geriatric patients 1978;57:186
  - cardiovascular effects, isoflurane and halothane 1975; 54:701
  - epidural anesthesia 1980;59:768
  - geriatrics, cardiovascular effects, isoflurane and halothane 1975;54:701
  - halothane
    - age-dependent responses to 1981;60:182
    - cardiovascular depression in infants 1982;61:42
  - ventilation
    - clinical significance of changes 1983;62:764
    - Innovar induced depression of, and chronic obstructive pulmonary disease 1977;56:826
- **Airway**
  - instrumentation, response following topical anesthesia with lidocaine 1980;59:123
  - laryngeal stenosis in acromegaly 1976;55:57
  - laryngotracheoesophageal cleft, airway management 1983;62:1041
  - obstruction
    - anesthetic management of patient with intratracheal mass 1977;56:295
    - caused by endotracheal tube cuff herniation 1978;57:114
    - from uvular edema in a pediatric patient 1983;62:1127
    - mediastinal Hodgkin's disease (case report) 1975;54:399
    - postintubation acute respiratory distress due to annular slough of laryngotracheal mucosa 1977;56:356
    - tests of, interrelationships and physiologic significance 1977;56:242
  - resistance
    - atropine and glycopyrrolate effects, lung mechanics 1981;60:85
    - changes following droperidol, hydroxyzine, and diazepam 1976;55:18
    - following endotracheal intubation, topical anesthesia 1980;59:270
  - tongue, phantom tongue pain and causalgia 1979;58:436
  - tracheal bronchus (brief reports) 1976;55:746
  - see Equipment
- **Albumin,** see Protein
- **Alcohol**
  - abuse, by anesthesia personnel 1983;62:467
  - alcoholism 1983;62:84
  - alcoholism, isoflurane requirements 1975;54:277
  - cross tolerance, cyclopropane (abstract) 1980;59:545

**Anesthesia**—*continued*
- ethanol administration, acute and chronic 1975;54:277
- ethanol increases serum $\beta$-endorphin in rats (abstract) 1980;59:537
- ethanol intoxication, prolonged effect on a full-term neonate (brief reports) 1976;55:602
- inhalation anesthetic potency, effects of ethanol, diazepam, and scopolamine on learning and memory compared to 1979;58:452
- injection, painful trigger points 1982;61:518
- intoxication, influence on anesthetic requirements and acute toxicity 1980;59:826
- memory and learning, compared to effects of ethanol, diazepam, and scopolamine 1979;58:452
- nerve block
  - abdominal pain and celiac plexus 1977;56:01
  - sciatic and femoral nerves 1981;60:532

**Alcuronium,** see Neuromuscular relaxants

**Aldosterone,** see Hormones

**Alfentanil,** see Analgesics

**Alkalosis,** see Acid-base equilibrium

**Allen's test,** see Arteries

**Allergy**
- allergic reactions during anesthesia 1983;62:341
- cephalothin, failure to produce anaphylaxis (letter) 1980;59:393
- cephapirin, anaphylactic reaction during spinal anesthesia 1979;58:337
- chymopapain (abstract) 1984;63:253
- chymopapain-induced hypotension 1984;63:533
- corticosteroids, ibuprofen, $H_2$ antagonists in allergic reactions (letter) 1983;62:857
- dextran 1975;54:40
- dextran (editor's choice) 1975;54:736
- etiology and guidelines for management 1976;55:493
- meperidine 1982;61:301
- neuromuscular relaxants, life-threatening anaphylactoid reactions 1983;62:559
- neuromuscular relaxants (letter) 1984;63:88
- pancuronium, anaphylactoid reactions 1984;63:865
- protamine, severe circulatory shock following 1980;59:77
- succinylcholine, anaphylaxis 1980;59:944
- succinylcholine (letter) 1981;60:456
- vancomycin, anaphylactoid reaction to, during anesthesia 1977;56:870

**Alopecia,** see Complications

**Alphaprodine,** see Anesthetics, intravenous

**Ambulatory anesthesia,** see Anesthesia, outpatient

**Aminophylline,** see Pharmacology

**4-Aminopyridine,** see Antagonists, neuromuscular relaxants

**Amitriptyline,** see Ataractics, antidepressants

**Amniotic fluid,** see
- Anesthesia, obstetric
- Embolism
- Uterus

**Amphetamine,** see Analeptics

**Ampules,** see Equipment

**Analeptics**
- amphetamine
  - abuse and obstetrical anesthesia (letter) 1980;59:710
  - cardiac arrest during cesarean section in abuser of 1979;58:528
- doxapram, cerebral and peripheral effects 1976;55:279

**Analgesia**
- acupuncture in obstetrics 1975;54:83
- cardiovascular effects of Innovar 1975;54:15
- caudal
  - for quadruplet delivery 1976;55:61
- doxapram
  - antagonism of meperidine-induced respiratory depression 1975;54:352
  - effects on cerebral blood flow and peripheral hemodynamics 1976;55:279
- epidural
  - bacteriologic aspects 1976;55:187
  - inadequate 1975;54:593
- local, supplemented by "pentazepam" for laparoscopic sterilization 1976;55:177
- methoxyflurane, administration for vaginal delivery or cesarean section 1976;55:415
- minimal analgesic quantities of Innovar, fentanyl and droperidol in man 1975;54:15
- narcotic versus post-thoracotomy intercostal block 1976;55:542
- neurolept, analgesia for awake pronation of surgical patients 1977;56:276
- postoperative, epidural morphine for pain after cesarean delivery 1983;62:666
- postoperative thoracotomy 1975;54:773
- regional, bacteriologic aspects 1976;55:187
- regional following epidural blood patch 1975;54:634

**Analgesics**
- abuse
  - anesthesiology and addiction 1983;62:465
  - by anesthesia personnel 1983;62:467
  - drug addiction, brief reports 1975;54:158
  - drug addiction, current perspective 1976;55:582
  - drug addiction, treating acute heroin and methadone toxicity (editor's choice) 1976;55:607
- alfentanil
  - (abstract) 1984;63:265
  - and obesity (abstract) 1983;62:251
  - anesthetic induction 1982;61:267
  - catecholamine and cortisol responses to coronary artery surgery (abstract) 1982;61:177
  - comparison with opioids for valvular heart surgery 1984;63:1081
  - hemodynamic changes during rapid induction of anesthesia (abstract) 1983;62:276
  - pharmacokinetics 1982;61:657
  - pharmacokinetics before and after cardiopulmonary bypass (abstract) 1983;62:266
  - variable rate infusion as a supplement to nitrous oxide 1983;62:982
- bremazocine, sedation and analgesia without respiratory depression 1983;62:483
- buprenorphine, epidural use for postoperative analgesia 1984;63:593
- butorphanol (abstract) 1984;63:243, 270
- and morphine
  - parenteral analgesic activity 1976;55:394
  - anesthesia (letter) 1982;61:624
  - common bile duct pressure changes 1984;63:441
  - comparison with morphine 1983;62:78
  - effects on adrenergic function in saphenous veins 1983;62:21
  - effects on intrabiliary tract dynamics 1984;63:139
  - hemodynamic effects in dogs 1981;60:715
- caffeine, effects on cardiac acceleration response to noxious stimulation 1984;63:669
- codeine, comparison with acupuncture on postoperative dental pain 1977;56:473
- dezocine
  - interaction with morphine 1983;62:899
  - postoperative, comparison with meperidine 1978;57:563
- effect on recovery from anesthesia in rats 1975;54:97
- epidural, narcotics, postoperative analgesia 1980;59:473
- fenoprofen, management of postoperative pain 1982;61:1002
- fentanyl
  - (abstract) 1984;63:183, 192, 236
  - age effects (abstract) 1982;61:171
  - aging and pharmacokinetics 1982;61:968

anesthetic requirements and cardiovascular effects 1978;57:411
aortocoronary bypass surgery 1981;60:412
as supplement to nitrous oxide anesthesia 1984;63:405
awareness and recall 1980;59:948
biliary spasm and fentanyl 1981;60:638
blood pressure response and plasma concentrations during high- and very high-dose anesthesia 1983;62:661
bradycardia after (letter) 1980;59:162
bradycardia induced by, central vagal control of, during halothane anesthesia 1978;57:31
cardiac surgery (abstract) 1982;61:206
cardiac surgery in infants 1984;63:117
cardiovascular effects and catecholamine responses 1981;60:563
cesarean section (abstract) 1982:61:179
common bile duct pressure changes 1984;63:441
comparison with opioids for valvular heart surgery 1984;63:1081
convulsions 1982;61:1020
coronary bypass surgery (abstract) 1980;59:562
dental surgery 1980;59:775
EEGs during high doses 1984;63:386
effect on adrenergic function in canine arteries 1981;60:21
effect on arginine vasopressin and cortisol secretion 1984;63:25
effect on temperature gradients in cardiac surgical patients 1983;62:1002
effects during experimental ischemia 1980;59:644
effects on hemodynamics and plasma catecholamine 1983;62:305
effects on intrabiliary tract dynamics 1984;63:139
effects on somatosensory cortical-evoked potentials 1984;63:833
effects on stress-induced elevation of plasma vasopressin (ADH) after surgery 1983;62:727
gastric fluid volume after 1980;59:287
hepatotoxicity 1984;63:1076
interaction with diazepam during coronary artery surgery 1983;62:881
large single dose for coronary artery surgery 1982;61:521
low dose (abstract) 1982;61:168
nalbuphine-reversed respiratory depression 1984;63:814
negative inotropic effect 1984;63:97
nitrous oxide and, cardiovascular effects on dogs 1976;55:168
nitrous oxide and, correlation of oxygen uptake and cardiovascular dynamics during 1978;57:37
PDA ligation in infants (abstract) 1980;59:557
placental passage and uterine effects 1983;62:894
plasma, cardiovascular stability (abstract) 1982;61:188
plasma concentrations and influence of nitrous oxide on cardiovascular responses 1979;58:390
postintubation hypertension 1982;61:680
preloading for rapid-sequence induction 1984;63:60
reduced painful tooth pulp sensations 1982;61:751
reduction of postintubation hypertension (abstract) 1981;60:264
rigidity and pulmonary compliance 1983;62:332
somatosensory cortical evoked potential alteration (abstract) 1980;59:544
ventilatory depression during and after anesthesia in humans 1983;62:966
heroin
  extradural diamorphine and stress 1982;61:15
  lumbar extradural effects 1984;63:629
hydromorphone, in cardiac surgery 1984;63:55
lofentanil, dosage and CNS opiate receptor binding 1983;62:705
meperidine
  allergy to 1982;61:301
  as supplement to nitrous oxide anesthesia 1984;63:405
  common bile duct pressure changes 1984;63:441
  comparison, labor pain (abstract) 1982;61:187
  comparison of effects on pulmonary function with post-thoracotomy intercostal block 1976;55:542
  gastric levels in surgical patients 1979;58:88
  generalized cardiovascular and regional effects in conscious dogs 1981;60:649
  induced respiratory depression, doxapram antagonism 1975;54:352
  methotrimeprazine and, balanced anesthesia 1975;54:749
  neonatal electroencephalographic patterns as affected by maternal administration of 1978;57:303
  nitrous oxide, cardiovascular effects in dog 1977;56:836
  obstetric 1982;61:652
  pancuronium 1977;56:669
  postoperative, comparison with dezocine 1978;57:563
methadone, neurological effects (abstract) 1980;59:531
  toxicity and heroin, treatment (editor's choice) 1976;55:607
morphine
  (abstract) 1984;63:210, 277
  alone and with scopolamine and atropine as intravenous surgical premedicants 1977;56:606
  antagonistic effect on positive inotropic response of ouabain, rabbit heart 1975;54:787
  as supplement to nitrous oxide anesthesia 1984;63:405
  awareness and dreams, with diazepam in nitrous oxide anesthesia 1976;55:702
  bupivacaine-morphine epidural anesthesia for prostatectomy 1981;60:818
  butorphanol and, parenteral analgesic activity 1976;55:394
  cardiovascular effects of patients with coronary artery disease 1982;61:109
  cesarean section (abstract) 1982;61:190
  circulatory responses to, influence of barbiturate anesthetic induction on 1977;56:615
  common bile duct pressure changes 1984;63:441
  compared with intramuscular narcotic and intercostal nerve block for postoperative pain relief 1982;61:93
  comparison to lidocaine as adjunct to diazepam-nitrous oxide, cardiac 1980;59:130
  comparison with butorphanol 1983;62:78
  continuous infusion technique 1984;63:757
  EEGs during high doses 1984;63:386
  effect of hydroxyzine 1980;59:690
  effect on ventilatory $CO_2$ sensitivity 1983;62:633
  effects on adrenergic function in saphenous veins 1983;62:21
  effects on cardiac acceleration response to noxious stimulation 1984;63:669
  effects on somatosensory cortical-evoked potentials 1984;63:833
  epidural 1982;61:236
  epidural, side effects 1982;61:174, (abstract) 1982;61:490
  for postoperative analgesia in the grossly obese 1984;63:583
  hemodynamic effects, cardiac surgery 1976;55:47
  interaction with nalbuphine in rats 1981;60:629
  labor (abstract) 1982;61:190
  (letter) 1984;63:375
  lumbar extradural effects 1984;63:629
  management of postoperative pain 1982;61:1002

- **Analgesics**—*continued*
  - morphine—*continued*
    - maternal and neonatal effects 1984;63:319
    - myocardial infarction size, rats 1982;61:843
    - myocardial oxygen consumption 1982;61:979
    - perineural injection 1983;62:164
    - postoperative pain 1981;60:726
    - postsurgical low back pain syndrome (abstract) 1982;61:191
    - promethazine and, as premedicants 1977;56:801
    - reduction of detrusor tone (letter) 1984;63:464
    - relief of postoperative pain after cesarean delivery 1983;62:666
    - renal function 1975;54:357
    - respiratory depression after epidural morphine 1984;63:08
    - respiratory depression after (letter) 1982;61:70
    - respiratory depression following bilateral carotid endarterectomy 1981;60:64
    - spinal (abstract) 1982;61:188
    - transient neurologic changes after (letter) 1981;60:540
    - urine norepinephrine excretion, cardiopulmonary bypass 1975;54:509
    - urodynamic effects and naloxone reversal 1983;62:641
  - nalbuphine
    - anesthetic potency and interaction with morphine in rats 1981;60:629
    - effects on adrenergic function in saphenous veins 1983;62:21
    - effects on intrabiliary tract dynamics 1984;63:139
    - reflex activity and (abstract) 1982;61:184
    - reverses fentanyl respiratory depression 1984;63:814
  - narcotic
    - basic constraints 1981;60:461
    - bilary tract, pressure changes in guinea pigs by anesthetics 1979;58:120
    - biliary spasm and fentanyl 1981;60:638
    - catecholamine release with morphine and diazepam 1981;60:406
    - epidural morphine for postoperative pain relief 1982;61:93
    - extradural diamorphine and stress 1982;61:15
    - meperidine, pharmacokinetics of high-dose 1981;60:08
    - reduction of postintubation hypertension (abstract) 1981;60:264
    - respiratory depression following bilateral carotid endarterectomy 1981;60:64
    - total anesthesia with sufentanil (abstract) 1981;60:276
    - pentazepam (pentazocine plus diazepam) supplementing local analgesia for laparoscopic sterilization 1976;55:177
  - pentazocine
    - for postoperative pain relief 1983;62:949
    - diazepam and, supplementing local analgesia 1976;55:177
  - receptors 1984;63:143
  - role in anesthesiology 1980;59:874
  - sufentanil
    - as supplement to nitrous oxide anesthesia 1984;63:405
    - cardiovascular effects of 1982;61:115
    - catecholamine and cortisol responses to, coronary artery surgery (abstract) 1982;61:177
    - comparison with opioids for valvular heart surgery 1984;63:1081
    - EEGs during high doses 1984;63:386
    - effect on minimum alveolar anesthetic concentration 1983;62:987
    - for cardiac surgery in infants 1984;63:117
    - hormonal effects of (abstract) 1982;61:214
    - influence on endocrine and metabolic responses to cardiac surgery 1983;62:391
    - total narcotic anesthesia (abstract) 1981;60:276
  - theoretic significance of pH dependence of narcotics and narcotic antagonists 1976;55:253
  - ventilatory arrest after 1977;56:727
- **Anaphylaxis,** see Allergy
- **Anatomy**
  - brachial plexus, surface landmarks for supraclavicular block of 1982;61:28
  - celiac plexus, and ganglia, normal variations 1979;58:461
  - dorsalis pedis artery, blood pressure in great toe with simulated occlusion of 1978;57:453
  - epidural space, correlation of skin–space distance with physical parameters (letter) 1984;63:539
  - glomus bodies, glomus jugulare tumors 1983;62:686
  - ligamentum flavum, in epidural anesthesia 1984;63:499
  - sciatic nerve, block 1980;59:371
  - subarachnoid space, distance from the skin in an obstetric population 1983;62:944
- **Anemia,** see Blood
- **Anesthesia**
  - acid-base disorders 1975;54:299
  - acupuncture, a clinical study 1976;55:508
  - acute ethanol intoxication, effect on neonate (brief reports) 1976;55:602
  - analysis of tasks and human factors for coronary artery bypass 1976;55:374
  - anaphylaxis management 1976;55:493
  - biliary tract surgery, biliary spasm and fentanyl 1981;60:638
  - 1-bromo-1,2,2-trifluorocyclobutane (42M-9) uptake and excretion in man, comparative study on pharmacokinetics and metabolism of inhalation anesthetics 1976;55:853
  - cardiovascular
    - (abstract) 1984;63:181, 232, 271
    - afterload reduction and preload augmentation 1980;59:737
    - anesthetic induction with alfentanil 1982;61:267
    - anesthetic management of the first permanent, orthotopic, prosthetic cardiac replacement 1984;63:685
    - antidiuretic and growth hormone responses following sufentanil and alfentanil in man 1982;61:434
    - assessment and reversal of heparin-induced anticoagulation for cardiopulmonary bypass 1983;62:710
    - butorphanol and morphine 1983;62:78
    - catecholamine changes during cardiopulmonary bypass (abstract) 1981;60:272
    - catecholamine release with morphine and diazepam 1981;60:406
    - catheter complications 1984;63:772
    - changes in mixed venous and coronary sinus $P_{50}$ 1980;59:751
    - comparison of fentanyl, sufentanil, and alfentanil for valvular heart surgery 1984;63:1081
    - comparison of halothane and fentanyl effects on temperature gradients 1983;62:1002
    - comparison of lidocaine and morphine as adjunct 1980;59:130
    - complications in surgery for congenital heart disease 1984;63:657
    - continuous postoperative measurement of venous oxygen saturation 1984;63:873
    - coronary-artery bypass, analysis of tasks and human factors in anesthesia 1976;55:374
    - coronary blood flow, $MVO_2$, and hemodynamics (abstract) 1981;60:266
    - criteria for early extubation after surgery 1977;56:703
    - cryptenamine, and control of hypertension during bypass 1978;57:54
    - diazepam and diazepam–nitrous oxide effects, coronary artery

  disease 1980;59:438
  dobutamine and myocardial metabolism 1982;61:917
  drug therapy of ischemic myocardium 1982;61:10
  early diagnosis of myocardial ischemia 1981;60:789
  EEG changes due to unsuspected aortic dissection 1984;63:946
  effect of calcium-entry blockers 1984;63:515
  effect of methohexital infusion 1983;62:317
  effect of nitroglycerin on large airways 1983;62:421
  effects during high- and very high-dose fentanyl anesthesia 1983;62:661
  effects of calcium chloride 1984;63:723
  effects of fentanyl, and anesthetic requirements 1978;57:411
  effects of nitrous oxide on myocardial metabolism and hemodynamics 1984;63:1071
  effects of pancuronium and vecuronium 1983;62:1059
  effects of sufentanil 1982;61:115
  exaggerated chamber enlargement in Ebstein's anomaly 1981;60:909
  fentanyl infusion 1982;61:972
  fentanyl, large single-dose 1982;61:521
  fentanyl–air–oxygen anesthesia for preterm infants 1981;60:331
  halothane, blood solubility during bypass, with crystalloid hemodilution and hypothermia 1977;56:622
  hemodynamic calculations (letter) 1980;59:519
  hemodynamic responses to anesthetic induction with midazolam or diazepam 1981;60:802
  hemodynamic tracking system 1980;59:169
  hydromorphone for CABS 1984;63:55
  hypotension following bypass 1975;54:482, 1977;56:720
  influence of sufentanil on endocrine and metabolic responses to cardiac surgery 1983;62:391
  inhalational anesthesia for coronary revascularization (letter) 1983;62:1047
  Innovar 1975;54:15
  intraaortic balloon counterpulsation for right heart failure 1980;59:74
  isoflurane and halothane to control hypertension 1983;62:15
  isoflurane in ischemic heart disease 1984;63:635
  long-term metoprolol therapy and neuroleptanesthesia in coronary artery surgery 1983;62:380
  metabolism after acute $\beta$-adrenergic blockade (letter) 1984;63:540
  mitral and aortic valvular disease 1982;61:788
  monitoring of femoral artery pressure during replacement of aneurysm of descending thoracic aorta 1977;56:603
  myocardial damage following bypass, with halothane 1977;56:556
  myocardial function during halothane and enflurane 1980;59:240
  myocardial oxygen consumption with halothane and morphine 1982;61:979
  narcotic anesthesia in infants 1984;63:117
  narcotic requirements 1984;63:101
  nitroglycerin and myocardial metabolism 1982;61:828
  oxygen–fentanyl anesthesia in patients with poor left ventricular function 1983;62:476
  oxygen–high dose fentanyl–droperidol for aortocoronary bypass surgery 1981;60:412
  patient transport following open heart surgery (abstract) 1981;60:238
  patients with cold autoimmune disease 1984;63:349
  pediatric fentanyl dosing 1984;63:577
  plasma fentanyl concentrations and influence of nitrous oxide 1979;58:390
  platelet involvement in coagulation time 1984;63:394
  preoperative estimation of risk in cardiac surgery 1981;60:625
  propranolol and circulatory responses 1981;60:579
  protamine sulfate and myocardial metabolism 1982;61:247
  scavenging of potassium cardioplegic solution 1983;62:780
  superior vena caval obstruction during heart surgery 1983;62:941
  temperature changes and ventilation (abstract) 1983;62:283
  use of propranolol to control rate–pressure product 1981;60:732
  vasodilation by nitroprusside vs nitroglycerin 1982;61:256
  vasospastic angina after calcium injection 1984;63:1124
dental
  and anesthesia (correspondence) 1978;57:751
  cardiovascular effects of cannabinol during oral surgery 1976;55:203
  catecholamine response to oral surgery 1984;63:640
  hazard during orthognathic surgery 1980;59:150
  intravenous sedation, local anesthesia 1980;59:775
  ketamine 1975;54:248
  nitrous oxide and neurologic disease 1981;60:297
  prolonged apnea after succinylcholine (case history) 1976;55;737
  settlement in cardiac arrest case (physician and the law) 1975;54:398
depth
  correlation of oxygen uptake and cardiovascular dynamics during $N_2O$–fentanyl and $N_2O$–thiopental, in dog 1978;57:37
  dreams and awareness, effect of morphine, diazepam, nitrous oxide 1976;55:702
  during high-dose fentanyl–diazepam–oxygen anesthesia 1983;62:698
  patient awareness 1983;62:239
  recall and perioperative awareness 1976;55:513
duration 1984;63:353
  local anesthetics, bupivacaine mixed with chloroprocaine 1979;58:364
electroshock
  (abstract) 1984;63:244
  arterial blood gas analyses 1975;54:203
  autonomic blockade and cardiovascular and catecholamine response 1977;56:46
  intraocular pressure during anesthesia 1975;54:479
  (letter) 1984;63:1140
epilepsy, methohexital 1982;61:997
evaluation, preoperative (abstract) 1982;61:219
geriatric, cardiac dysrhythmia following reversal of neuromuscular blocking agents 1978;57:186
gynecologic, during menses (questions and answers) 1977;56:746
neurosurgical
  cardiovascular and cation effects of urea 1981;60:641
  cardiovascular effects during cerebral aneurysm surgery 1983;62:742
  cordotomy 1984;63:1036
  effect of the seated position 1983;62:648
  for transsphenoidal surgery of hypophyseal region 1978;57:206
  in sitting position (correspondence) 1977;56:325
  intracranial arteriovenous malformation in infancy 1977;56:236
  lidocaine or thiopental, intracranial hypertension 1980;59:435
  methohexital in epilepsy 1982;61:997
  prevention of blood pressure response to skull-pin head holder 1979;58:241
  propranolol premedication and hypotension 1984;63:125

- **Anesthesia**—*continued*
  - neurosurgical—*continued*
    - reversible evoked potential changes 1981;60:835
    - risk of paradoxical air embolism 1984;63:429
  - obstetric
    - (abstract) 1984;63:256
    - acid-base equilibrium in diabetic parturients 1982;61:662
    - acid-base status, maternal and neonatal and bupivacaine concentration in diabetic parturients 1981;60:574
    - acupuncture 1975;54:83
    - acute ethanol intoxication, prolonged effect on neonate (brief reports) 1976;55:602
    - amniotic fluid embolism during curettage for missed abortion 1977;56:739
    - anesthesia training centers in the U.S.A.—1975 1976;55:839
    - anesthetics and murine intelligence 1981;60:794
    - anesthetics in infants with breast feeding (questions and answers) 1977;56:744
    - atropine and glycopyrrolate, cardiovascular effects of 1983;62:426
    - bearing down and incidence of spinal headache 1981;60:524
    - bupivacaine, compared with etidocaine for vaginal delivery 1975;54:250
    - caudal analgesia for quadruplet delivery 1976;55:61
    - cesarean section, effect of morphine-diazepam 1976;55:702
    - chloroprocaine, paracervical block with 1977;56:709
    - cimetidine as an oral antacid 1983;62:720
    - comparison of general anesthesia and lumbar epidural analgesia for elective cesarean section 1977;56:228
    - continuous infusion epidural analgesia 1984;63:421
    - effect of halothane on cardiac output and regional blood flow 1983;62:489
    - effect on maternal plasma beta-endorphin levels (abstract) 1983;62:245
    - effect of morphine–diazepam on awareness and dreams of patients under nitrous oxide anesthesia for cesarean section 1976;55:702
    - effects on neonatal behavior 1984;63:301
    - elimination of metabolites after epidural anesthesia with 2-chloroprocaine 1983;62:1089
    - enflurane analgesia 1981;60:133
    - enflurane with uterine contractility in rabbits 1978;57:160
    - epidural anesthesia for cesarean section 1983;62:914
    - epidural anesthesia for elective cesarean section 1984;63:623
    - epidural anesthesia for cesarean section in kyphoscoliosis 1978;57:125
    - epidural anesthesia, maternal, fetal, and neonatal responses 1982;61:638
    - epidural morphine, maternal and neonatal effects of 1984;63:319
    - etidocaine compared with bupivacaine, for vaginal delivery 1975;54:250
    - fetal anesthetic requirement for halothane 1983;62:09
    - fetal oxygenation 1982;61:576
    - fetal heart rate, effect of lumbar epidural anesthesia 1975;54:779
    - for combined cesarean section and excision of pheochromocytoma 1978;57:276
    - glucose homeostasis, maternal-fetal 1982;61:32
    - halothane, enflurane, and isoflurane for cesarean delivery 1983;62:516
    - halothane, maternal, reduces cerebral blood flow in acidotic sheep fetus 1980;59:35
    - hemodynamic effects and placental transfer of atropine and glycopyrrolate in the pregnant ewe 1981;60:710
    - hyperbaric bupivacaine for spinal anesthesia in cesarean section 1984;63:1009
    - hyperbaric, bupivacaine peridural 1978;57:593
    - hypokalemia associated with terbutaline 1980;59:917
    - increasing oxygenation during cesarean section (questions and answers) 1977;56:463
    - intravenous albumin administration, spinal hypotension 1980;59:655
    - ketamine, arterial blood gases during vaginal delivery 1978;57:121
    - ketamine, thiopental, and extradural anesthesia, neonatal neurobehavioral tests after 1977;56:548
    - left-sided chest pain with radiation to shoulder after vaginal delivery 1977;56:863
    - (letter) 1984;63:1045
    - lidocaine and 2-chloroprocaine 1983;62:168
    - lidocaine and bupivacaine for cesarean section, neonatal neurobehavioral responses after 1984;63:413
    - local anesthetics 1976;55:829
    - lumbar epidural anesthesia, effect on fetal heart rate 1975;54:779
    - lumbar sympathetic block with bupivacaine 1978;57:486
    - management of a parturient with cardiac valve prosthesis 1976;55:214
    - maternal and fetal effects of prophylactic hydration before epidural anesthesia 1983;62:673
    - maternal and infant neutrophil chemotaxis (abstract) 1980;59:543
    - maternal, fetal, and neonatal effects of lidocaine–epinephrine 1984;63:973
    - lidocaine and bupivacaine for cesarean section, neonatal neurobehavioral responses after 1984;63:413
    - lidocaine, neonatal neurobehavioral effects of 1983;62:473
    - meperidine-bupivacaine 1982;61:652
    - metabolic acidosis 1980;59:929
    - methoxyflurane analgesia, fluoride levels in parturients and neonates following 1977;56:646
    - mitral and aortic valvular disease 1982;61:788
    - morphine-diazepam, effect on awareness and dreams of patients for cesarean section 1976;55:702
    - myasthenia gravis and pregnancy 1978;57:441
    - neonatal electroencephalographic patterns as affected by maternal drugs during labor and delivery 1978;57:303
    - neonatal gastric pH 1978;57:98
    - newborn hypoventilation 1975;54:38
    - nitroglycerin therapy for hypertension, pregnant ewes 1980;59:494
    - organization of neonatal resuscitation equipment (letter) 1979;58:442
    - pain control in parturition (correspondence) 1977;56:598
    - peridural, comparison of spread in pregnant and nonpregnant women 1978;57:544
    - pharmacokinetics of etidocaine in fetal and neonatal lambs and adult sheep 1982;61:104
    - physostigmine, reversal of sedation in parturients 1976;55:478
    - placental passage and uterine effects of fentanyl 1983;62:894
    - placental transfer of midazolam 1984;63:31
    - plasma and cerebrospinal fluid endorphin levels 1982;61:893
    - postpartum deterioration in valvular heart disease (letter) 1983;62:460
    - postpartum hypertension and convulsion after oxytocic drugs 1976;55:813
    - preeclampsia–eclampsia 1983;62:590

  prehydration fluids and lactate and pyruvate concentrations 1984;63:69
  prolonged neuromuscular blockade with succinylcholine 1983;62:444
  prophylactic ephedrine and cesarean section 1982;61:839
  pulmonary venous admixture in sheep 1979;58:318
  relief of postoperative pain after cesarean delivery 1983;62:666
  renal function following methoxyflurane administration 1976;55:415
  self-administered methoxyflurane and trichloroethylene, medical and legal aspects (questions and answers) 1977;56:322
  side brace for the delivery room table (letter) 1984;63:1046
  spread of epidural anesthesia 1981;60:421
  succinylcholine–vecuronium for cesarean section 1983;62:909
  terbutaline therapy 1980;59:391
  the first experiment (letter) 1983;62:1136
  use of succinylcholine (letter) 1983;62:1051
  uterine contractions and epidural block 1982;61:127
  vaginal delivery, renal function following methoxyflurane administration 1976;55:415
  with epidermolysis bullosa 1978;57:281
ophthalmologic, myocardial infarction following local anesthesia 1980;59:257
orthopedic, intraoperative awakening for possible early recognition of neurologic sequelae, Harrington rod spinal fusion 1976;55:526
orthopedic (letter) 1984;63:372
orthopedic, wake-up technique to avoid neurologic sequelae during Harrington rod procedure 1977;56:733
otolaryngologic
  anesthesia for patient with tracheal T-tube stent 1981;60:218
  continuous etomidate infusion 1982;61:993
  diagnostic bronchoscopy 1980;59:585
  intravenous procaine as supplement 1979;58:492
  management of pediatric patient with tracheal T-tube 1981;60:445
outpatient (abstract) 1984;63:282
  digit-symbol test and dot test, comparison for street fitness of outpatients 1976;55:883
  evaluation, anesthesiologist 1976;55:307
  guidelines 1982;61:921
  neuromuscular recovery after laparoscopy 1984;63:51
  preanesthetic glycopyrrolate and cimetidine 1984;63:40
  test to assess recovery 1979;58:324
pediatric 1983;62:124, 1984;63:359
  advantages of infant ventilators over adapted adult ventilators 1976;55:769
  age-dependent responses to halothane 1981;60:182
  atracurium, pharmacology of 1984;63:309
  blood pressure, measurement in neonates and infants utilizing an automatic noninvasive oscillometric monitor 1981;60:742
  blood pressure measurement (letter) 1982;61:956
  bronchopleural-cutaneous fistula, bronchial blockade (brief reports) 1976;55:874
  cardiopagus in neonatal thoracopagus twins 1980;59:304
  cardiovascular surgery, ketamine-pancuronium-narcotic 1975;54:800
  caudal, in infants 1977;56:686
  caudal block, bupivacaine compared with etidocaine 1975;54:250
  closed circuit anesthesia 1984;63:765
  Columbia pediatric circle, humidity output (brief reports) 1976;55:877
  compressed air-$O_2$-anesthetic mixtures for neonate 1977;56:127
  congenital complete heart block 1979;58:334
  congenital heart disease, complications in surgery for 1984;63:657
  congenital lobar emphysema (case history) 1976;55:869
  congenital tracheal stenosis, resection of 1979;58:431
  craniopagus twins, separation of 1980;59:883
  dentistry, ketamine 1975;54:248
  *d*-tubocurarine, neonatal responses to 1984;63:799
  Doppler-assisted radial artery cannulation 1984;63:346
  electroconvulsive therapy, arterial blood gas analyses 1975;54:203
  enflurane anesthesia, intraocular pressure 1975;54:212
  epiglottitis management 1975;54:622
  ethanol intoxication (brief reports) 1976;55:602
  fentanyl dosing during cardiac surgery 1984;63:577
  fentanyl–air–oxygen anesthesia for ligation of patent ductus arteriosus 1981;60:331
  foreign body hazard in neonate 1977;56:726
  halothane anesthesia and cardiovascular depression in infants 1982;61:42
  halothane, hemodynamic effects of 1984;63:731
  halothane-induced complications 1984;63:838
  halothane, uptake and distribution of 1983;62:404
  heart defect surgery, hypothermia 1975;54:660
  high-frequency jet ventilation for tracheal resection 1984;63:1039
  humidification (brief reports) 1976;55:877
  hypothermia during cytoscopy (brief reports) 1976;55:592
  in perspective 1978;57:634
  induction in infant with frontonasal dysplasia and meningo-encephalocele 1977;56:736
  induction techniques, behavioral consequences of 1977;56:538
  intracranial arteriovenous malformation in infancy 1977;56:236
  intramuscular, radiotherapy 1976;55:92
  intraocular pressure 1976;55:773
  isoflurane, cardiovascular effects of inhalation induction with 1983;62:411
  isoflurane, minimum anesthetic concentration of 1984;63:418
  ketamine and intraocular pressure 1976;55:773
  ketamine, hemodynamic effects of 1984;63:895
  ketamine-pancuronium-narcotic, cardiovascular surgery 1975;54:800
  (letter) 1984;63:1140
  lumbar epidural anesthesia, effect on fetal heart rate 1975;54:779
  malignant hyperthermia in a six-month-old infant 1978;57:262
  mechanical ventilation with a nonbreathing system (abstract) 1980;59:565
  mobile respiratory assistor, for neonatal transport 1978;57:729
  muscle relaxants in 1981;60:335
  muscle relaxants, comparison of non-depolarizing 1981;60:862
  narcotic anesthesia for cardiac surgery 1984;63:117
  neonatal gastric pH 1978;57:98
  neuromuscular parameters (abstract) 1981;60:251
  new endotracheal tube (brief reports) 1975;54:273
  newborn hypoventilation 1975;54:38
  nitrous oxide
    absorption and excretion 1976;55:95
    encephalography 1976;55:402
  pancuronium for cardiac anesthesia 1981;60:798
  postintubation croup 1977;56:501

- **Anesthesia**—*continued*
  - pediatric—*continued*
    - preextubation ventilatory measurements 1980;59:467
    - radiotherapy, intramuscular ketamine 1976;55:92
    - Rees gas scavenger (brief reports) 1976;55:881
    - Rees system safety valve (brief reports) 1976;55:741
    - regional anesthesia 1975;54:387
    - respiratory pattern, change in, affect dead space/tidal volume ratio 1980;59:341
    - respiratory weaning of intubated newborns and infants (abstract) 1981;60:239
    - Romano-Ward syndrome, effects of stellate ganglion block on the idiopathic prolongation of the Q-T interval with cardiac arrhythmia 1976;55:782
    - severe hypertension 1976;55:519
    - subacute upper respiratory infection 1979;58:331
    - succinylcholine 1980;59:639, (abstract) 1980;59:535
    - succinylcholine and thiopental, effect of, on potassium concentrations 1984;63:1146
    - succinylcholine, characteristics of neuromuscular blockade with, in neonates 1978;57:63
    - systems, waste gas scavenging valve for 1977;56:291
    - tubes, endotracheal (brief reports) 1975;54:273
    - unrelenting hypotension associated with an acute abdomen in a comatose hemophiliac child 1976;55:346
    - use of laryngoscope (letter) 1983;62:241
    - vecuronium, safety and efficacy of 1983;62:1083
  - scheduling, operating room, by computer 1977;56:831
  - therapeutic
    - left stellate ganglion block for hypertension (abstract) 1981;60:269
    - stellate ganglion, convulsions during block 1979;58:329
    - stellate ganglion, treatment of hypertension after coronary artery surgery (abstract) 1981;60:269
  - thoracic
    - circulatory collapse after pneumonectomy 1977;56:451
    - comparison of ketamine and enflurane 1984;63:521
    - high-frequency jet ventilation in a child 1984;63:1039
    - high-frequency positive pressure ventilation in open-chest surgery 1981;60:324
    - improved oxygenation during thoracotomy with selective PEEP to dependent lung 1977;56:26
    - one-lung high-frequency positive pressure ventilation 1981;60:683
    - oxygen-jet ventilation during tracheal reconstruction 1977;56:429
  - veterinary, pentobarbital and fetal survival (correspondence) 1977;56:472
  - volatile, halothane, and nitroprusside-induced hypotension, effect on renal function 1978;57:521
- **Anesthesia Foundation,** see Organizations
- **Anesthesiologists**
  - analysis of tasks and human factors for coronary-artery bypass 1976;55:374
  - auditing performance 1984;63:611
  - causes of death 1981;60:01
  - drug abuse 1983;62:467
- **Anesthesiology** 1983;62:124
  - auditing, performance 1980;59:465
  - audits, computerized (abstract) 1981;60:262
  - history, publications and 1980;59:01
  - journals, abstracts, papers resulting from 1982;61:445
  - journals, citation analysis, publications resulting from anesthesia meeting abstracts 1982;61:445
  - journals (letter) 1982;61:1024, 1984;63:90, 374, 538
  - journals, relationship between author and editor (editor's choice) 1976;55:22
  - journals, righting the wrongs of writing, copy editors speak out (editor's choice) 1976;55:219
  - numenon and the phenomenon 1975;54:257
  - practice, survey 1975;54:112
- **Anesthetic techniques**
  - balanced
    - aging and fentanyl pharmacokinetics 1982;61:968
    - (letter) 1984;63:1049
    - methotrimeprazine and meperidine 1975;54:749
    - questions and answers 1976;55:907
  - Bird Mark-14 ventilator (brief reports) 1976;55:379
  - brachial plexus, surface landmarks for supraclavicular block of 1982;61:28
  - cardiac disease 1976;55:617
  - cardiac surgery following propranolol 1975;54:571
  - circle systems, comparison of efficiency 1976;55:724
  - closed circle, compromise for 1978;57:18
  - closed circuit
    - in infants and children 1984;63:765
    - vaporizer performance 1980;59:359
  - dissociative
    - digitalis tolerance 1975;54:106
    - emergence from ketamine anesthesia 1975;54:169, 312
    - ketamine 1975;54:35
    - ketamine, intravenous, arterial hypoxemia 1976;55:311
    - ketamine, intraocular pressure in children 1976;55:773
    - ketamine in pediatric dentistry 1975;54:248
    - ketamine tolerance 1976;55:778
    - ketamine-induced, neural mechanisms 1975;54:189
    - ketamine-pancuronium-narcotic 1975;54:800
  - dosage nomogram for sodium nitroprusside-induced hypotension 1976;55:574
  - doxapram, effects on cerebral blood flow and peripheral hemodynamics 1976;55:279
  - effect of general agents, ouabain, and aldosterone on striated muscle contraction in toad 1976;55:409
  - electroanesthesia, monkey 1976;55:536
  - electronarcosis, current applications to produce general and local anesthesia 1977;56:678
  - endobronchial
    - arterial oxygenation during one-lung anesthesia 1980;59:847
    - circulatory collapse after pneumonectomy 1977;56:451
    - comparison of ketamine and enflurane 1984;63:521
    - double-lumen tube adapter 1980;59:507
    - double-lumen tubes (letter) 1984;63:882
    - intubation for intraoperative protection 1976;55:340
    - jet ventilation of one lung 1984;63:957
    - one-lung anesthesia 1982;61:507
    - one-lung pediatric anesthesia 1981;60:450
  - endotracheal
    - awake 1975;54:323
    - changing tubes 1978;57:737
    - criteria for extubation after intracardiac surgery 1977;56:703
    - deglutition of tube: case report 1978;57:590
    - difficult extubation, endotracheal tube cuff (brief reports) 1976;55:876
    - laryngotracheal residue 1976;55:392
    - lidocaine spray 1975;54:438
    - low- and high-pressure tube cuffs, tracheal pathology following short-term intubation with 1978;57:577
    - nasotracheal extubation, unusual problem (brief reports) 1976;55:302
    - noninvasive assessment, by capacitance respirometry of respiration 1975;54:807
    - spontaneous extubation 1977;56:293

epidural
  absorption of lidocaine 1979;58:360
  (abstract) 1984;63:184, 196
  accidental subdural local anesthetic injection 1983;62:1124
  after total hip replacement 1983;62:174
  age and dose response (abstract) 1981;60:268
  age and spread of solution 1980;59:768
  aging (abstract) 1980;59:553
  anatomy of ligamentum flavum 1984;63:499
  anesthesia, spinal subdural hematoma associated with 1980;59:72
  anesthetic spread (letter) 1981;60:227
  anticoagulants and 1980;59:394
  assessment of motor blockade during epidural anesthesia 1983;62:889
  baroreflex control of heart rate 1983;62:815
  basic constraints of 1981;60:461
  bedbug infestation as complication (letter) 1979;58:531
  biliary tract surgery 1982;61:793
  block, complicating lumbar sympathetic block 1977;56:873
  block, use of Tuohy needle in paramedian approach 1977;56:582
  blood patch for postspinal headache 1984;63:1121, (letter) 1984;63:962
  blood patch (letter) 1981;60:123
  blood patches, safe volume for (letter) 1983;62:619
  bupivacaine, effect of lateral position (abstract) 1983;62:273
  bupivacaine for cesarean section 1980;59:89
  bupivacaine-morphine epidural anesthesia for prostatectomy 1981;60:818
  buprenorphine for postoperative analgesia 1984;63:593
  cardiac effects 1984;63:817
  cardiovascular responses to clamping of the aorta 1979;58:372
  catheters, prevention of external kinking 1977;56:865
  caudal anesthesia in infants 1977;56:686
  caudal, concentration and extent of sensory spread 1984:63:1017
  cesarean section (abstract) 1982;61:210
  comparison of spread in pregnant and nonpregnant women 1978;57:544
  continuous infusion in labor and delivery 1984;63:421
  continuous infusion of morphine 1984;63:757
  correlation of skin–space distance with physical parameters (letter) 1984;63:539
  delayed onset of anesthesia in patients with back pain 1981;60:874
  dynamics of local anesthetic compounds 1977;56:110
  effect of position on anesthetic spread 1984;63:863
  effects of extradural morphine and heroin 1984;63:629
  effects on neonatal behavior 1984;63:301
  elimination of CABA after anesthesia with 2-chloroprocaine during parturition 1983;62:1089
  etidocaine, prolonged spinal nerve involvement after 1978;57:361
  extradural diamorphine and stress 1982;61:15
  fetal oxygenation 1982;61:576
  flaccid paraparesis following obstetrical anesthesia, possible role of benzyl alcohol 1977;56:219
  for elective cesarean section (letter) 1984;63:623
  for patients with chronic neurological disease (letter) 1983;62:620
  for postoperative analgesia in the grossly obese 1984;63:583
  herpes simplex virus infection (letter) 1982;61:714
  Horner's syndrome following obstetric extradural block 1980;59:299
  hyperbaric bupivacaine, in obstetrics 1978;57:593
  hypotensive, adenosine triphosphate-induced 1984;63:381
  hypotensive, trimethaphan-induced vasodilation 1984;63:290
  in patients with multiple sclerosis (letter) 1983;62:856
  intravascular migration of catheter (letter) 1979;58:252, 443, 531
  intravenous regional, evaluation of the myotoxicity of bupivacaine in bier block 1983;62:796
  laryngoscopy, fentanyl and postintubation hypertension 1982;61:680
  latent dural puncture after lumbar block 1977;56:725
  lateral position 1978;57:95
  (letter) 1984;63:375, 783
  lidocaine 1983;62:447
  low pressure headache following 1980;59:799
  lumbar, fetal heart rate baseline variability 1975;54:779
  lumbar, multiple sclerosis 1982;61:1022
  maternal and neonatal acid-base status and bupivacaine concentration in diabetic parturients 1981;60:574
  maternal, fetal, and neonatal effects of lidocaine–epinephrine 1984;63:973
  maternal, fetal, and neonatal responses 1982;61:638
  meperidine-bupivacaine for obstetrics 1982;61:652
  modified Dawkins epidural indicator (letter) 1979;58:350
  modified Dawkins epidural indicator, teaching aid 1978;57:738
  monitoring sensory level (letter) 1981;60:694
  morphine (abstract) 1983;62:258
  morphine 8, respiratory depression after (abstract) 1984;63:262
  morphine for labor and delivery 1984;63:319
  morphine for postoperative analgesia 1982;61:236
  morphine for postoperative pain relief 1982;61:93
  morphine, side effects 1982;61:490
  narcotics, effects on stress-induced elevation of plasma vasopressin (ADH) after surgery 1983;62:727
  narcotics (letter) 1981;60:123
  narcotics, postoperative analgesia 1980;59:473
  needle bevel direction (abstract) 1982;61:208
  neonatal behavioral tests after extradural anesthesia 1977;56:548
  neonatal neurobehavioral effects of lidocaine 1983;62:473
  neonatal neurobehavioral responses after lidocaine and bupivacaine for cesarean section 1984;63:413
  neurologic deficits following 1981;60:150
  neutrophil chemotaxis, influence of anesthesia on1978;57:567
  patch, spinal subdural epiarachnoid hematoma 1980;59:702
  pentazocine for postoperative pain 1983;62:949
  plasma concentrations of lidocaine 1983;62:578
  plastic syringes (letter) 1980;59:805
  position and spread of anesthesia 1981;60:584
  postoperative pain relief with morphine 1981;60:726
  potential for contamination of continuous catheters 1977;56:222
  precordial chest pain during anesthesia (letter) 1983;62:1134
  reduction of detrusor tone (letter) 1984;63:464
  respiratory depression after epidural morphine 1984;63:08
  spread and uterine contractions (abstract) 1981;60:277
  spread in pregnancy (letter) 1979;58:350

**Anesthetic techniques**—*continued*
  epidural—*continued*
    spread of epidural anesthesia 1981;60:421
    steroid effect on nerves and meninges 1980;59:610
    successful anesthesia following epidural blood patch 1978;57:272
    sympathetic recovery following lumbar epidural and spinal analgesia 1977;56:352
    test doses (letter) 1981;60:616
    transient lower extremity weakness 1981;60:527
    transient neurologic changes after morphine (letter) 1981;60:540
    22-gauge needle 1978;57:743
    uterine contractions and spread of local anesthetics 1982;61:127
  hypotensive
    (abstract) 1984;63:207, 213, 280, 281
    adenosine, adenosine triphosphate, and sodium nitroprusside 1982;61:273
    adenosine- and ATP-induced (letter) 1984;63:538
    adenosine triphosphate and sodium nitroprusside, cardiovascular changes in rat 1982;61:99
    arterial and venous dilation (abstract) 1981;60:248
    blood pressure determines blood loss 1980;59:203
    cardiac failure and valvular regurgitation patients 1980;59:737
    cardiovascular effects during cerebral aneurysm surgery 1983;62:742
    consumption of vitamin $B_{12}$ (abstract) 1980;59:538
    cryptenamine, control of hypertension during cardiopulmonary bypass 1978;57:54
    experience with nitroprusside and epidural analgesia in a pregnant quadriplegic patient 1981;60:61
    hemodynamic and sympathoadrenal responses (abstract) 1981;60:249
    hydralazine, intraoperative hypotension (abstract) 1982;61:192
    hydralazine, neurosurgery 1982;61:1016
    induced hypotension, effect of propranolol 1979;58:466
    induced hypotension, hemodynamic consequences of withdrawal of nitroprusside or nitroglycerin 1982;61:261
    induced hypotension, sodium nitroprusside 1976;55:654
    induction, RO 21-3981, intravenous, for premedication and 1978;57:01
    infraclavicular plexus block, pain relief after mastectomy 1982;61:986
    infrarenal aortic clamping (abstract) 1981;60:242
    MAC and deliberate hypotension 1981;60:513
    neurologic changes caused by nitroprusside (abstract) 1980;59:561
    nitroglycerin 1983;62:421
    nitroglycerin, arterial and venous dilation (abstract) 1981;60:248
    nitroglycerin and myocardial metabolism 1982;61:828
    nitroglycerin during infrarenal aortic clamping (abstract) 1981;60:242
    nitroglycerin hemodynamic and sympathoadrenal responses (abstract) 1981;60:249
    nitroglycerin in patient with variant angina 1980;59:707
    nitroglycerin, intrapulmonary shunting during induced hypotension 1982;61:231
    nitroglycerin therapy for hypertension, pregnant ewes 1980;59:494
    nitroglycerin, vasodilation 1982;61:256
    nitroprusside (abstract) 1983;62:252
    nitroprusside, and cerebral blood flow (correspondence) 1978;57:142
    nitroprusside and mitral stenosis 1980;59:662
    nitroprusside and thiosulfate in dogs 1982;61:120
    nitroprusside blood pressure response to laryngoscopy and tracheal intubation 1979;58:116
    nitroprusside, changing renal blood following, in nephrolithotomy 1977;56:102
    nitroprusside, cyanide intoxication induced by 1977;56:533
    nitroprusside, dose requirement reduced with increasing halothane concentrations 1978;57:457
    nitroprusside, during anesthesia and operation in the head-up position 1977;56:391
    nitroprusside, drug therapy of ischemic myocardium 1982;61:10
    nitroprusside effect on myocardial $O_2$ consumption (abstract) 1980;59:554
    nitroprusside, effect on renal function 1978;57:521
    nitroprusside, failure of cyanide to antagonize 1980;59:672
    nitroprusside for intraoperative hypertension (correspondence) 1977;56:748
    nitroprusside, intraoperative hypertension 1976;55:880
    nitroprusside, intrapulmonary shunting during induced hypotension 1982;61:231
    nitroprusside, myocardial revascularization (abstract) 1982;61:215
    nitroprusside, pulmonary vascular response to, in anesthetized dogs 1978;57:551
    nitroprusside therapy in oliguric patient, cyanide production during 1977;56:729
    nitroprusside used to attenuate blood pressure response 1979;58:116
    nitroprusside, using enflurane and morphine 1979;58:174
    nitroprusside, vasodilation 1982;61:256
    nitroprusside-induced hypotension 1976;55:654
    prevention of nitroprusside toxicity with thiosulfate (abstract) 1980;59:547
    propranolol attenuates renin release 1981;60:569
    propranolol premedication 1984;63:125
    pseudo resistance to nitroprusside (letter) 1980;59:518
    reflex responses to sodium nitroprusside and control by cryptenamine 1980;59:909
    regional blood flow activity 1984;63:503
    renal perfusion, mannitol, and (letter) 1979;58:156
    tracheobronchial cytologic changes 1980;59:197
  insufflation 1984;63:368
  ketamine-pancuronium-narcotic cardiovascular 1975;54:800
  laryngoscopy
    for tracheal intubation, blood pressure and heart rate changes during, influence of lidocaine 1978;57:197
  laser surgery 1981;60:885
  morphine
    bupivacaine–morphine epidural anesthesia for prostatectomy 1981;60:818
  neurolept analgesia for awake pronation of surgical patients 1977;56:276
  paracervical lidocaine and 2-chloroprocaine 1983;62:168
  regional
    abdominal pain, alcohol celiac plexus nerve block 1977;56:01
    (abstract) 1984;63:259
    age effects on pH of cerebrospinal fluid and vasopressors 1975;54:455
    ankle, model for comparison of local anesthetics 1982;61:418
    axillary block 1983;62:215
    axillary, model for comparison of local anesthetics 1982;61:418
    block 1975;54:250
    brachial plexus 1983;62:55 1984;63:363
    brachial plexus, cardiac arrest after interscalene block 1977;56:446

  brachial plexus, continuous block for prolonged sympathectomy and pain control 1978;57:128
  brachial plexus, factors influencing distribution of local anesthetic 1979;58:225
  brachial plexus, hoarseness and Horner's syndrome after interscalene block 1977;56:585
  brachial plexus, landmarks for infraclavicular block 1977;56:554
  brachial plexus, longitudinal supraclavicular approach for insertion of plastic cannulas 1981;60:352
  brachial plexus, parascalene technique 1979;58:267
  brachial plexus, using omotrapezoid route 1977;56:486
  brachial plexus, vascular insufficiency following axillary block 1981;60:162
  brachial plexus block, surface landmarks for 1982;61:28
  bupivacaine 1976;55:763
  bupivacaine compared with etidocaine 1975;54:250
  bupivacaine compared with tetracaine 1976;55:489
  bupivacaine, review of cases 1978;57:42
  caudal analgesia, quadruplet delivery 1976;55:61
  celiac plexus, block, and pancreatic arteriovenous malformation 1977;56:288
  celiac plexus, hepatotoxicity 1984;63:479
  celiac plexus, normal anatomic variations 1979;58:461
  cervical plexus block 1975;54:370
  children 1975;54:387
  chloroprocaine (letter) 1984;63:544
  comparison of insulated and uninsulated needles for locating peripheral nerves 1984;63:925
  comparison of insulated vs uninsulated needles for electrical nerve location 1984;63:919
  competitive neuromuscular 1975;54:649
  continuous brachial plexus block, clinical and anatomical study 1984;63:680
  epidural blood patch 1975;54:459, 634
  epidural blood patch, regional analgesia 1975;54:634
  epidural injection, inadvertent, thiopental (brief reports) 1975;54:406
  epidural lumbar anesthesia, effect on fetal heart rate 1975;54:779
  epidural, morbid obesity 1980;59:902
  epinephrine, catecholamine response to oral surgery 1984;63:640
  evaluation of memory 1976;55:368
  femoral, lower extremity surgery 1980;59:631
  intercostal block (abstract) 1983;62:246
  intercostal block, hemodynamic changes after, with bupivacaine-epinephrine 1978;57:492
  intercostal block, postoperative thoracotomy 1975;54:773
  intercostal block, post-thoracotomy 1976;55:542
  intercostal block, spread and uptake of solution injected (abstract) 1980;59:553
  intercostal nerve block, a roentgenographic anatomic study 1980;59:815
  interscalene cervical plexus 1975;54:370
  intravenous, onset and progression with dilute lidocaine 1982;61:834
  lateral femoral cutaneous, inadvertent "3-in-1-block" 1980;59:887
  lidocaine and 2-chloroprocaine 1983;62:168
  lumbar disc surgery 1976;55:550
  lumbar puncture, CSF cutaneous fistula (case history) 1975;54:691
  lumbar sympathetic block, single needle approach 1975;54:725
  lumbar sympathetic block, with bupivacaine, analgesia for labor 1978;57:486
  lumbar sympathetic block, peridural block complicating 1977;56:873
  lumbar sympathetic block, single needle approach 1975;54:725
  lumbosacral plexus block, unusual complication 1976;55:350
  lumbosacral plexus block 1976;55:350
  lumbosacral plexus block, unusual complication 1976;55:350
  medullary narcosis (editor's choice) 1975;54:579
  obstetrics 1976;55:829
  paracervical block with chloroprocaine 1977;56:709
  penis, nerve block for postoperative pain relief in children 1978;57:495
  peridural, comparison of solutions used in lumbar and caudal anesthesia 1978;57:175
  peripheral nerve block, bupivacaine 1976;55:763
  pharmacokinetics, of local anesthetics during plexus blocks 1977;56:852
  renal transplantation 1976;55:69
  sacral nerve block for bladder pain 1982;61:46
  sciatic block, popliteal fossa 1980;59:371
  sciatic–femoral nerve block 1975;54:489
  sciatic-femoral, supine approach 1975;54:489
  sensory block, tetanic electrical current quantification 1980;59:796
  spinal accessory nerve, simple technic for block 1978;57:591
  splanchnic block, study of technique and spread of solution 1981;60:369
  stellate ganglion block 1975;54:567
  sympathectomy, measurement with pulse-wave monitor 1975;54:289
  sympathetic block, ejaculatory failure 1984;63:770
  sympathetic block, paravertebral (correspondence) 1978;57:145
  transsacral block (letter) 1982;61:623
  versus general (questions and answers) 1976;55:277
spinal
  absorption of lidocaine 1979;58:360
  (abstract) 1984;63:238, 267
  acid–base equilibrium in diabetic parturients 1982;61:662
  after laminectomy (letter) 1981;60:169
  albumin, prevention of spinal hypotension, cesarean 1980;59:655
  anatomy of ligamentum flavum 1984;63:499
  backache, a contraindication to spinal anesthesia (questions and answers) 1975;54:505
  basic constraints of 1981;60:461
  bearing down and incidence of headache in parturients 1981;60:524
  bevel and deflection of spinal needles (letter) 1983;62:371
  blood levels during 1979;58:357
  bronchospasm during 1981;60:839
  bupivacaine compared with tetracaine 1980;59:743
  bupivacaine versus tetracaine spinal 1976;55:550
  cervical plexus block, single injection technique 1975;54:370
  cesarean section, cerebral infarction following 1982;61:390
  clonic convulsions after 1982;61:945
  comparison of neural blockade and pharmacokinetics after subarachnoid lidocaine 1983;62:995
  dibucaine and tetracaine 1982;61:133
  distance from skin to the lumbar epidural space 1983;62:944
  dose–response study of bupivacaine 1983;62:931
  easy approach (letter) 1981;60:770
  effect of added epinephrine with lidocaine 1981;60:417, (abstract) 1981;60:275
  effect of age, pH of cerebrospinal fluid and vasopressors 1975;54:455
  effect of cough 1979;58:306
  effect of hyperbaric bupivacaine with added vasoconstrictors 1982;61:49

- **Anesthetic techniques**—*continued*
  - spinal—*continued*
    - effects of epinephrine (letter) 1981;60:913
    - effects of epinephrine on lidocaine (letter) 1984;63:542
    - effects of phenylephrine and neural blockade 1984;63:129
    - epidural abscess following 1978;57:351
    - epinephrine and (letter) 1982;61:395
    - esophageal rupture 1983;62:606
    - evaluation, rhesus monkey 1981;60:756
    - hairshaft in subarachnoid space (letter) 1981;60:694
    - heparinization, operational (questions and answers) 1975;54:506
    - high spinal anesthesia (abstract) 1980;59:561
    - hyperbaric bupivacaine for spinal anesthesia in cesarean section 1984;63:1009
    - introducers for 25-gauge spinal needles (letter) 1983;62:1046
    - isobaric (letter) 1982;61:714
    - isobaric tetracaine and lithotomy position 1981;60:810
    - (letter) 1984;63:783, 1140
    - for pediatric surgery (letter) 1984;63:782
    - lumbar disc surgery, spinal anesthesia 1976;55:550
    - lumbar puncture, CSF cutaneous fistula (case history) 1975;54:691
    - meningitis as a complication 1983;62:513
    - monitoring sensory level (letter) 1981;60:694
    - morphine for transurethral prostatectomy (abstract) 1983;62:255
    - neurologic deficits following 1981;60:150
    - neurotoxicity after injection of large volumes of local anesthetic solutions 1983;62:802
    - neutrophil chemotaxis, influence of anesthesia on 1978;57:567
    - normal human cerebrospinal fluid and tetracaine density 1981;60:814
    - patient heparinized (questions and answers) 1975;54:506
    - patients with previous lumbar laminectomy or fusion (abstract) 1980;59:529
    - percutaneous catheterization (letter) 1981;60:618
    - persistent neurologic deficit and adhesive arachnoiditis following chloroprocaine 1980;59:452
    - pharmacokinetics of lidocaine, rhesus monkey 1982;61:746
    - postural puncture headache, chronic pain 1980;59:772
    - postural puncture headache 1982;61:948
    - precordial chest pain during anesthesia (letter) 1983;62:1134
    - previous lumbar laminectomy 1980;59:881
    - prolonged sensory/motor deficits following 1980;59:399
    - prophylactic ephedrine and cesarean section 1982;61:839
    - pruritis following 1980;59:157
    - spinal taps (letter) 1982;61:309
    - subarachnoid hematoma after lumbar puncture 1983;62:777
    - subarachnoid injection of autologous blood and neurologic deficits 1981;60:603
    - subarachnoid intracranial pressure 1975;54:494
    - subdural hematoma, epidural anesthesia and continuous spinal anesthesia 1980;59:72
    - sympathetic recovery following lumbar epidural and spinal analgesia 1977;56:352
    - tetracaine and the effect of added vasoconstrictors 1983;62:793
    - uptake and elimination of local anesthetics 1983;62:1013
    - use of droperidol to control nausea 1984;63:85
    - vasoconstrictors 1984;63:134
  - topical
    - aerosol anesthesia of airway 1980;59:803
    - airway response to lidocaine 1980;59:123
    - bupivacaine anesthesia of the airway 1984;63:1001
- **Anesthetics, gases**
  - cyclopropane
    - halothane and, effect of dextroamphetamine and reserpine 1975;54:655
    - hypercapnia (brief reports) 1976;55:439
    - measurement of anesthetic potency 1981;60:380
    - used to test anesthetic potency in the elderly 1984;63:998
  - nitrous oxide
    - absorption and excretion 1976;55:95
    - absorption, endotracheal tube cuffs (brief reports) 1976;55:595
    - (abstract) 1984;63:175
    - abuse 1979;58:104
    - analgesic concentrations (letter) 1982;61:394
    - and halothane, neutrophil chemotaxis during 1977;56:696
    - and tympanic membrane rupture 1978;57:283
    - arterial oxygen tension in children (abstract) 1983;62:258
    - awareness and dreams of paitents for cesarean section, morphine-diazepam 1976;55:702
    - bactericidal effects 1979;58:136
    - barbiturate potency and nitrous oxide susceptibility 1984;63:35
    - carcinogenicity of 1978;57:678
    - cardiovascular effects of, during meperidine infusion 1977;56:836
    - cardiovascular response to exposure 1980;59:93
    - cardiovascular responses during halothane anesthesia 1978;57:84
    - cognitive reversal of expected analgesia 1983;62:1073
    - compared to enflurane analgesia in obstetrics 1981;60:133
    - cutaneous wound healing in presence of 1978;57:527
    - discontinuance does not prevent tension pneumocephalus 1981;60:57
    - effect of isoflurane anesthesia on blood flow 1983;62:499
    - effect of low concentration on rat fetus 1980;59:175
    - effect on accumulation rate and uptake of bowel gases 1979;58:405
    - effect on hemodynamic function during high-dose sufentanyl anesthesia (abstract) 1983;62:275
    - effect of oxygen 1976;55:734
    - effect on pulmonary vascular resistance (abstract) 1980;59:548 1983;62:257
    - effect on thymidine and methionine syntheses in pregnant rats 1983;62:738
    - effect on tracheal cilia 1980;59:426
    - effects of exposure 1984;63:526
    - effects on central sympathetic and vagal tone 1983;62:129
    - effects on monitoring performance and electroencephalogram (abstract) 1980;59:545
    - effects on muscle contractility 1984;63:451
    - effects on myocardial contractility 1984;63:47
    - effects on myocardial metabolism and hemodynamics 1984;63:1071
    - effects on ventilatory response to enflurane (abstract) 1981;60:261
    - encephalography, oxygen 1976;55:849
    - encephalography, pediatrics 1976;55:402
    - enflurane concentrations delivered by Ethrane vaporizers increased by 1979;58:30
    - enflurane vaporizer accuracy with (letters) 1979;58:440, 441
    - epinephrine-induced arrhythmias during halothane anesthesia, dogs 1982;61:414
    - expansion of intravitreal sulfur hexafluoride (abstract) 1983;62:290

  - exposure in operating room 1978;57:216
  - exposure to and neurologic disease among dental professionals 1981;60:297
  - fast oscillatory EEG activity induced by analgesic concentrations 1981;60:283
  - flow-directed catheters and (letter) 1982;61:308
  - hazards of use (editorial) 1979;58:73
  - hepatic clearance of lidocaine in dogs 1976;55:322
  - hepatotoxicity 1984;63:1076
  - inactivates methionine synthetase in human liver 1982;61:75
  - (letter) 1984;63:371
  - measurement of anesthetic potency 1981;60:380
  - memory effects (abstract) 1980;59:540
  - minimum alveolar concentration 1982;61:553
  - minimum alveolar concentrations in swine 1984;63:529
  - modification of halothane-altered renal function in dog 1977;56:690
  - oxygen 1976;55:849
  - patients with coronary artery disease 1980;59:438
  - patients with mitral stenosis and pulmonary hypertension 1980;59:323 (abstract) 0546
  - pediatrics 1976;55:402
  - plasma fentanyl concentration and influence of, on cardiovascular responses 1979;58:390
  - potencies in mice bred for resistance or susceptibility 1981;60:646
  - pulmonary air embolism and (letter) 1982;61:956
  - simplified technic of air encephalography (correspondence) 1977;56:469
  - supression of spinal evoked EEG potentials in surgical patients (abstract) 1983;62:267
  - tolerance tested in mice 1981;60:137
  - tolerance, withdrawal convulsions following nitrous oxide 1980;59:19
  - vaporizer aberrance (letter) 1983;62:956
  - vaporizer outputs and (letter) 1980;59:808
  - venous air embolism 1982;61:304
  - viscosity effects in anesthesia 1980;59:192
  - volumes, absorbed and excreted 1976;55:95
  - with fentanyl and with thiopental, correlation of oxygen uptake and cardiovascular dynamics, in dog 1978;57:37
- trace concentrations
  - faulty anesthesia circuits, source of pollution 1977;56:359
  - in sperm (abstract) 1981;60:281
  - mechanical aspects of pollution control 1977;56:769
  - monitoring occupational exposure 1977;56:778
  - nitrous oxide exposure in operating room 1978;57:216
  - NO and $NO_2$, effects of exposure 1984;63:526
  - operating room pollution, governmental perspectives and guidelines 1977;56:775
  - psychomotor performance after exposure to 1979;58:475
  - recovery room air pollution (letter) 1980;59:711
  - scavenging of (letter) 1980;59:163
  - toxicity 1978;57:328
  - when vaporizer is off 1977;56:793

**Anesthetics, intravenous**
- alfentanil
  - (abstract) 1984;63:279, 284
  - antidiuretic and growth hormone responses 1982;61:434
  - comparison with opioids for valvular heart surgery 1984;63:1081
  - comparison with thiopental 1984;63:330
  - effect on plasma hormonal changes, early postoperative respiratory function, and speed of postoperative recovery (abstract) 1983;62:285
  - induction with 1982;61:267
- alphaprodine, and renal blood flow autoregulation, compared with halothane or methoxyflurane in dog 1978;57:389
- diazepam
  - negative inotropic effect 1984;63:97
  - plasma levels 1975;54:173
  - renal hemodynamics 1982;61:853
- droperidol
  - and pheochromocytoma (letter) 1981;60:770
  - comparison with diazepam and hydroxyzine as premedication 1977;56:496
  - during cesarean section (letter) 1984;63:782
  - effects of ketamine in heart disease 1983;62:193
- hydroxyzine, and diazepam
  - changes in airway resistance 1976;55:18
  - hypoxic ventilation 1984;63:106
  - or diazepam, respiratory function following premedication with 1978;57:695
  - premedication (correspondence) 1978;57:288
  - prevention and treatment of nausea and vomiting 1979;58:396
  - to control nausea 1984;63:85
- etomidate
  - (abstract) 1984;63:225
  - cardiovascular and pulmonary responses in cardiac patients 1979;58:40
  - clinical and EEG comparison with thiopental 1977;56:479
  - clinical use for anesthesia induction 1976;55:730
  - clinical use of, for induction 1976;54:687
  - continuous infusion for $CO_2$ laser surgery of the larynx 1982;61:993
  - effect on cardiovascular system 1977;56:717
  - increased cerebrospinal fluid pressure 1975;54:687
  - infusion regimen for hypnosis 1983;62:654
  - inotropic and anesthetic potencies 1983;62:961
- etoxadrol hydrochloride, new intravenous anesthetic 1976;55:335
- fentanyl
  - (abstract) 1984;63:181, 261, 266
  - aging and pharmacokinetics 1982;61:968
  - and convulsions (letter) 1983;62:858
  - anesthetic requirements and cardiovascular effects 1978;57:411
  - antidiuretic and growth hormone responses 1982;61:434
  - a periodic analysis of EEG response during open heart surgery (abstract) 1983;62:284
  - blood pressure response and plasma concentrations during high- and very high-dose anesthesia 1983;62:661
  - bradycardia induced by, central vagal control of, during halothane anesthesia 1978;57:31
  - cardiovascular effects 1979;58:179
  - cardiovascular effects and catecholamine responses 1981;60:563
  - cardiovascular effects of pancuronium and vecuronium 1983;62:1059
  - choledochoduodenal sphincter spasm (abstract) 1981;60:257
  - comparison with opioids for valvular heart surgery 1984;63:1081
  - during pediatric cardiac surgery 1984;63:577
  - effect on arginine vasopressin and cortisol secretion 1984;63:25
  - effect on myocardial metabolism and hemodynamic responses in coronary patients (abstract) 1983;62:276
  - effect on the rate of CSF production 1983;62:581
  - effects on EEG 1984;63:489

- **Anesthetic, intravenous**—*continued*
  - fentanyl—*continued*
    - effects on myocardial contractility 1984;63:47
    - for ligation of patent ductus arteriosus in preterm infants 1981;60:331
    - halothane metabolite binding in obesity 1981;60:548
    - hemodynamics (abstract) 1983;62:245
    - hepatotoxicity 1984;63:479
    - induced hepatic injury 1983;62:155, 140, 146
    - infusion for aortocoronary bypass surgery 1982;61:972
    - intraoperative effectiveness in balanced anesthesia (abstract) 1983;62:259
    - narcotic requirements 1984;63:101
    - negative inotropic effect 1984;63:97
    - nitrous oxide and, cardiovascular effects 1976;55:168
    - nitrous oxide and, correlation of oxygen uptake and cardiovascular dynamics during 1978;57:37
    - oxygen-fentanyl anesthesia in patients with poor left ventricular function 1983;62:476
    - plasma catecholamine levels 1982;61:366
    - renal function and stress response 1981;60:552
    - rigidity and hypercarbia associated with (letter) 1981;60:362
  - fentanyl–droperidol, for aortocoronary bypass surgery 1981;60:412
  - hydromorphone, in cardiac surgery 1984;63:55
  - Innovar
    - cardiovascular effects 1975;54:15
    - digitalis tolerance 1975;54:106
    - intraocular pressure during anesthesia in adult ophthalmic surgery 1980;59:50
    - microdrip technique: double blind study 1977;56:279
    - premedication, refusal of surgery 1975;54:224
  - ketamine
    - (abstract) 1984;63:186
    - and pancuronium-narcotic, cardiovascular surgery 1975;54:800
    - anesthesia and hemorrhage 1981;60:481
    - anesthesia, emergence 1975;54:169
    - arterial blood gases and, during vaginal delivery 1978;57:121
    - arterial hypoxemia 1976;55:311
    - cardiopulmonary responses to, in noncardiac patients 1977;56:813
    - cardiovascular dynamics, halothane and enflurane anesthesia 1975;54:588
    - cardiovascular effects 1980;59:355
    - cardiovascular effects following aminophylline 1982;61:685
    - comparison with enflurane 1984;63:521
    - comparison with procaine and lidocaine in histamine-induced contracture of guinea pig tracheal muscle 1978;57:25
    - direct effects on isolated canine cerebral and mesenteric arteries 1983;62:553
    - effect on endotoxin-induced lung injury 1983;62:398
    - effects of droperidol in heart disease 1983;62:193
    - effects on brainstem auditory evoked potentials 1982;61:338
    - effects on mood 1984;63:1087
    - effects on peripheral sympathetic nervous system, guinea pig 1980;59:45
    - emergence 1975;54:169
    - encephalopathy, infant 1982;61:873
    - failure to alleviate carcinoid syndrome 1980;59:621
    - for treatment of penile erection (letter) 1983;62:457
    - hazards in ischemic heart disease (letter) 1983;62:1044
    - hemodynamic effects in hypovolemic dogs (abstract) 1983;62:247
    - in children with congenital heart disease 1984;63:895
    - in dermolytic bullous dermatosis 1977;56:398
    - Innovar and, anesthesia effect on digitalis tolerance 1975;54:106
    - interaction with neuromuscular blocking agents in phrenic nerve-hemidiaphragm preparation of rat 1978;57:238
    - intraocular pressure, in children 1976;55:773
    - intravenous 1976;55:311
    - multiple anesthetics 1975;54:35
    - neonatal neurobehavioral tests after 1977;56:548
    - microdrip technique, double blind study 1977;56:279
    - patient preference 1975;54:35
    - pediatric dentistry 1975;54:248
    - pediatric radiotherapy 1976;55:92
    - physostigmine antagonized 1980;59:764
    - plasma levels 1982;61:87
    - recall following, for open-heart surgery 1978;57:267
    - renal hemodynamics 1982;61:853
    - rhesus monkey 1975;54:189
    - subdissociative dosage, emergence phenomena 1975;54:312
    - suppression of chemically induced convulsions in infant cockerel 1980;59:406
    - tolerance 1976;55:788
  - laryngeal stenosis in acromegaly 1976;55:57
  - lidocaine, comparison to morphine as adjunct to diazepam-nitrous oxide, cardiac 1980;59:130
  - lofentanil, dosage and CNS opiate receptor binding 1983;62:705
  - methohexital
    - epilepsy 1982;61:997
    - hemodynamic and hepatic effects 1983;62:317
    - uncontrolled epilepsy (abstract) 1982;61:185
  - midazolam, circulatory responses 1983;62:135
  - morphine
    - cardiopulmonary bypass 1975;54:509
    - cardiovascular responses to clamping of the aorta 1979;58:372
    - catecholamine release with diazepam 1981;60:406
    - comparison to lidocaine as adjunct to diazepam-nitrous oxide, cardiac 1980;59:130
    - effects of position (letter) 1984;63:169
    - myocardial oxygen consumption, afterload changes in dogs 1980;59:233
    - nitroprusside responses during 1979;58:174
    - postoperative analgesia (abstract) 1981;60:240
  - narcotics
    - continuous opioid infusion for scoliosis fusion surgery 1983;62:841
    - unconsciousness and amnesia 1983;62:625
  - neurolept, enzyme induction following surgery 1981;60:319
  - neurolepts, analgesia for awake pronation of surgical patients 1977;56:276
  - opioids
    - as supplement to nitrous oxide anesthesia 1984;63:405
    - effects on EEG 1984;63:386
  - pentobarbital
    - cardiovascular effects 1983;62:749
    - effects on brainstem auditory evoked potentials 1982;61:338
  - propanidid, test to assess recovery 1979;58:324
  - splanchnic circulation 1983;62:135
  - sufentanil
    - (abstract) 1984;63:250, 260, 261
    - antidiuretic and growth hormone responses 1982;61:434
    - cardiovascular effects of 1982;61:115
    - comparison with opioids for valvular heart surgery 1984;63:1081
    - influence on endocrine and metabolic responses to cardiac surgery 1983;62:391

  - plasma histamine levels during anesthesia for coronary bypass graft surgery (abstract) 1983;62:260
  - requirement of surgical anesthesia and effect on awakening time (abstract) 1983;62:292
- thiamylal
  - effects on central sympathetic and vagal tone 1983;62:129
  - influence of anesthetic induction on circulatory responses to morphine 1977;56:615
  - (letter) 1984;63:371
- succinylcholine, tracheal intubation 1976;55:232
- succinylcholine, with *d*-tubocurarine pretreatment and anesthetic induction 1976;55:77
- thiamylal-$N_2O$ halothane, influence of pancuronium or *d*-tubocurarine circulatory responses 1976;55:485
- thiopental
  - cardiovascular effects 1983;62:749
  - cholinergic action on hypothalamohypophyseal axis 1981;60:03
  - comparative hemodynamics with midazolam 1982;61:771
  - comparison with alfentanil 1984;63:330
  - comparison with fentanyl 1983;62:151
  - comparison with myocardial depressant action of halothane 1984;63:313
  - control of intracranial hypertension 1980;59:435
  - depression of lung mucociliary clearance by 1979;58:387
  - dose-response study in unpremedicated children (abstract) 1981;60:246
  - effects on mood 1984;63:1087
  - glucose tolerance and serum insulin levels 1975;54:718
  - halothane and enflurane protect against bronchospasm in asthma dog model 1978;57:629
  - hemodynamic effects of (abstract) 1981;60:260
  - hepatotoxicity 1984;63:1076
  - induced hepatic injury 1983;62:140, 146, 155
  - inotropic and anesthetic potencies 1983;62:961
  - naloxone fails to antagonize 1978;57:558
  - neonatal neurobehavioral tests after 1977;56:548
  - neuropsychiatric complications of bypass 1982;61:903
  - nitrous oxide and, correlation of oxygen uptake and cardiovascular dynamics during 1978;57:37
  - peripheral vascular resistance and venous capacitance changes during cardiopulmonary bypass (abstract) 1981;60:235
  - renal hemodynamics 1982;61:853
  - succinylcholine, and intraocular pressure 1975;54:471
  - suppression of nucleus reticularis gigantocellularis neurons 1982;61:763
  - test to assess recovery 1979;58:324

**Anesthetics, local**
- amide, toxicity of, dogs 1982;61:317
- antiarrhythmic, beta-adrenergic blockers 1981;60:897
- bupivacaine
  - (abstract) 1984;63:199, 212
  - arterial and venous plasma levels, peripheral nerve blocks 1976;55:763
  - compared with etidocaine for vaginal delivery 1975;54:250
  - as a topical anesthesia of the airway 1984;63:1001
  - assessment of motor blockade during epidural anesthesia 1983;62:889
  - benzodiazepine prophylaxis 1981;60:385
  - cardiotoxicity compared to lidocaine 1984;63:549
  - cardiotoxicity in adult sheep (abstract) 1983;62:268
  - cardiovascular effects of convulsant and supraconvulsant doses 1982;61:03
  - comparative CNS toxicity after rapid intravenous administration 1983;62:375
  - compared with tetracaine 1980;59:743
  - concentration and extent of sensory spread 1984;63:1017
  - continuous infusion in labor and delivery 1984;63:421
  - deaths from anesthetic-induced convulsions in mice 1980;59:401
  - determination by high-performance liquid chromatography 1984;63:448
  - differential blockade of isolated canine nerves 1983;62:754
  - differential effects of 1982;61:570
  - differential sensitivities of nerve fibers during pregnancy 1983;62:1070
  - dose–response for spinal anesthesia 1983;62:931
  - duration when mixed with chloroprocaine 1979;58:364
  - dynamics of, in compounds 1977;56:110
  - effect of epinephrine in prevention or correction of myocardial depression 1983;62:450
  - effect on neonatal neurobehavioral responses 1984;63:413
  - effects on cardiovascular function and plasma catecholamine levels 1984;63:1053
  - evaluation of analgesic effect and urinary excretion in man 1982;61:23
  - evaluation of the myotoxicity in bier blocks 1983;62:796
  - for spinal anesthesia in cesarean section 1984;63:1009
  - for use during cesarean section 1983;62:914
  - hepatotoxicity 1984;63:479
  - hyperbaric, peridural in obstetrics 1978;57:593
  - influence of diazepam on the serum protein binding 1984;63:980
  - influence on atria 1984;63:01
  - inhibits hydrolysis of chloroprocaine by human serum 1978;57:534
  - injection route alters toxicity 1980;59:925
  - local anesthetics in stimulus analgesia 1981;60:752
  - lumbar sympathetic block and: analgesia for labor 1978;57:486
  - mixture with chloroprocaine 1980;59:683
  - model for comparison in man 1982;61:418
  - neurotoxicity after injection of large volumes of local anesthetic solutions 1983;62:802
  - neurotoxicity in dogs 1982;61:279
  - resuscitation after overdose 1982;61:62
  - review of cases 1978;57:42
  - tracheal ring ciliary activity and 1978;57:448
  - treatment for convulsions and ventricular tachycardia 1984;63:856
  - trigger point therapy (abstract) 1981;60:251
- centbucridine 1983;62:109
- chloroprocaine
  - continuous infusion in labor and delivery 1984;63:421
  - control of pain 1981;60:112
  - cytotoxicity 1984;63:985
  - deaths from anesthetic-induced convulsions in mice 1980;59:401
  - duration of bupivacaine when mixed with 1979;58:364
  - dynamics of, in compounds 1977;56:110
  - for use during cesarean section 1983;62:914
  - in treatment of chronic pain (letter) 1981;60:844
  - injection route alters toxicity 1980;59:925
  - mixture with bupivacaine 1980;59:683
  - neurotoxicity after injection of large volumes of local anesthetic solutions 1983;62:802
  - paracervical block with 1977;56:709
  - persistent neurologic deficit and adhesive arachnoiditis following 1980;59:452

**Anesthetics, local**—*continued*
- chloroprocaine—*continued*
  - prolonged neural blockade 1980;59:447
  - prolonged neural blockade following (letter) 1980;59:808
  - prolonged sensory/motor deficits following 1980;59:399
  - toxicity, chloroprocaine and bupivacine in mice (letter) 1981;60:455
  - toxicity, chloroprocaine (letter) 1981;60:168
  - tracheal ring ciliary activity and 1978;57:448
  - with antioxidant sodium bisulfite 1984;63:445
- 2-chloroprocaine
  - comparison with lidocaine 1983;62:168
  - elimination of CABA after epidural anesthesia during parturition 1983;62:1089
  - hydrolysis of, by human serum, in presence of amide local anesthetics 1978;57:534
  - neurotoxicity (letters) 1982;61:155, 715
- 2-chloroprocaine-CE, neurotoxicity in dogs 1982;61:279
- cocaine (abstract) 1984;63:227
  - current perspective 1976;55:582
  - effect of intranasal administration on experimental pain in man 1982;61:358
  - lidocaine–phenylephrine as substitute 1984;63:915
- dextran interactions 1980;59:335
  - duration of rat infraorbital nerve block in combination with lidocaine or bupivacaine 1981;60:02
- diazepam and (abstract) 1980;59:540
- dibucaine, spinal anesthesia 1982;61:133
- differential sensitivity, margin of safety for transmission 1982;61:561
- dissociation constants, temperature dependence 1983;62:1025
- ester type, myasthenia gravis (questions and answers) 1975;54:506
- etidocaine
  - assessment of motor blockade during epidural anesthesia 1983;62:889
  - benzodiazepine prophylaxis 1981;60:385
  - cardiovascular effects of convulsant and supraconvulsant doses 1982;61:03
  - comparative CNS toxicity after rapid intravenous administration 1983;62:375
  - compared with bupivacaine for vaginal delivery 1975;54:250
  - differential effects of 1982;61:570
  - local anesthetics in stimulus analgesia 1981;60:752
  - pharmacokinetics, in fetal and neonatal lambs and adult sheep 1982;61:104
- lidocaine
  - absorption following subarachnoid and epidural administration 1979;58:360
  - (abstract) 1984;63:219, 224
  - adiposis dolorosa 1976;55:257
  - airway response following topical anesthesia with 1980;59:123
  - analgesic properties in mice 1979;58:85
  - as a topical anesthesia of the airway 1984;63:1001
  - as cocaine substitute 1984;63:915
  - benzodiazepine prophylaxis 1981;60:385
  - cardiotoxicity compared to bupivacaine 1984;63:549
  - cardiovascular effects of convulsant and supraconvulsant doses 1982;61:03
  - comparative CNS toxicity after rapid intravenous administration 1983;62:375
  - comparison to morphine as adjunct to diazepam-nitrous oxide, cardiac 1980;59:130
  - comparison with procaine and ketamine in histamine-induced contracture of guinea pig tracheal muscle 1978;57:25
  - concentration and extent of sensory spread 1984;63:1017
  - continuous infusion in labor and delivery 1984;63:421
  - control of intracranial hypertension 1980;59:435
  - controls extubation laryngospasm in children 1978;57:506
  - cytotoxicity 1984;63:985
  - deaths from anesthetic-induced convulsions in mice 1980;59:401
  - differential blockade of isolated canine nerves 1983;62:754
  - dynamics of, in compounds 1977;56:110
  - effect in allergic bronchoconstriction 1981;60:28
  - effect on neonatal neurobehavioral responses 1984;63:413
  - effects of pH on protein binding of 1978;57:478
  - effects of phenylephrine and neural blockade 1984;63:129
  - epinephrine-induced arrhythmias and, during enflurane anesthesia in man 1978;57:547
  - evaluation 1981;60:756
  - failure to trigger malignant hyperthermia 1979;58:99
  - for use during cesarean section 1983;62:914
  - hepatic clearance, nitrous oxide anesthesia 1976;55:322
  - influence on atria 1984;63:01
  - inhibits hydrolysis of chloroprocaine by human serum 1978;57:534
  - injection route alters toxicity 1980;59:925
  - interaction with epinephrine (correspondence) 1977;56:747
  - model for comparison in man 1982;61:418
  - myotoxicity in rats and humans 1981;60:471
  - neonatal neurobehavioral effects 1983;62:473
  - neural blockade and pharmacokinetics 1982;61:746
  - neuromuscular drug interactions 1980;59:678
  - neurotoxicity after injection of large volumes of local anesthetic solutions 1983;62:802
  - oropharyngeal, circulatory response to laryngoscopy and tracheal intubation with or without 1977;56:618
  - plasma concentrations following epinephrine-lidocaine injection 1978;57:724
  - plasma concentrations with cervical, thoracic, and lumbar epidural anesthesia 1983;62:578
  - potency of, in rat 1976;55:818
  - serum protein binding in humans 1981;60:395
  - topical, endotracheal spray 1975;54:438
  - tracheal ring ciliary activity and 1978;57:448
  - true water/oil partition coefficients of 1982;61:56
- magnesium enhances local nerve block 1984;63:111
- membrane-stabilizing actions and antiarrhythmic $\beta$-adrenergic blockers 1981;60:897
- mepivacaine
  - inhibits hydrolysis of chloroprocaine by human serum 1978;57:534
  - myotoxicity of single and repeated injections in rat 1980;59:275
  - vascular smooth muscle, rabbit 1982;61:756
- myotoxicity, regeneration of damaged muscle fibers 1980;59:727
- neuromuscular junction, interaction of muscle relaxants and local anesthetics at 1978;57:580
- neurotoxicity, in vivo study 1982;61:961
- obstetrics 1976;55:829
- peridural, comparison of solutions used in lumbar and caudal anesthesia 1978;57:175
- pH 1981;60:833
- pH (letter) 1980;59:892

- pharmacokinetics of, during plexus blocks 1977;56:852
- phenol, convulsions in celiac plexus block 1979;58:150
- potencies of 1982;61:01
- procaine
  - and tracheal ciliary ring activity 1978;57:448
  - comparison with lidocaine and ketamine in histamine-induced contracture of guinea pig tracheal muscle 1978;57:25
  - cytotoxicity 1984;63:985
  - in laryngeal papillomas in children 1979;58:492
  - pharmacokinetics in humans 1979;58:382
  - true oil/water partition coefficients of 1982;61:56
- pulmonary venous admixture in pregnant and nonpregnant sheep 1979;58:318
- tetracaine
  - comparative CNS toxicity after rapid intravenous administration 1983;62:375
  - compared with bupivacaine 1980;59:743
  - effect of added vasoconstrictors 1983;62:793
  - spinal anesthesia 1982;61:133
  - tetrahydrocannabinol 1976;55:203
  - versus bupivacaine spinal anesthesia 1976;55:489
- tetrodotoxin, action of 1976;55:568
- toxicity
  - chloroprocaine and bupivacaine in mice (letter) 1981;60:455
  - chloroprocaine (letter) 1981;60:168
  - effects of epinephrine (letter) 1984;63:702
  - neurologic deficits following epidural or spinal anesthesia 1981;60:150
  - reverse arterial blood flow as a pathway for 1978;57:428
  - systemic 1978;57:387

**Anesthetics, volatile**

- chloroform, measurement of anesthetic potency 1981;60:380
- dioxychlorane, correlation of anesthetic potency and lipid solubility 1981;60:201
- enflurane 1984;63:353
  - and halothane 1976;55:263
  - anesthesia and hemorrhage 1981;60:481
  - anesthetics and murine intelligence 1981;60:794
  - bactericidal effects 1979;58:136
  - blood-gas solubility 1982;61:941
  - calcium transport, sarcoplasmic reticulum 1982;61:142
  - carcinogenicity of 1978;57:678
  - cardiac decompensation (case history) 1976;55:433
  - cardiovascular effects 1979;58:179
  - cardiovascular effects during controlled ventilation 1978;57:619
  - cardiovascular effects, enflurane and halothane 1976;55:85
  - cardiovascular effects of metocurine with 1978;57:540
  - cardiovascular effects 1976;55:85
  - cardiovascular effects, patients with coronary artery disease (abstract) 1980;59:536
  - changes in blood chemistries 1976;55:547
  - comparative study using systolic time intervals 1976;55:262
  - comparison with ketamine 1984;63:521
  - COPD 1976;55:806
  - discoloration of (letter) 1981;60:843
  - disposition in the obese (abstract) 1980;59:562
  - effect of ketamine on cardiovascular dynamics 1975;54:588
  - effect of ouabain tolerance 1976;55:360
  - effect of subanesthetic concentrations on behavior 1978;57:434
  - effect on tracheal cilia 1980;59:426
  - effects on blood pressure 1984;63:482
  - effects on brainstem auditory evoked responses 1982;61:968
  - effects on drug metabolism 1984;63:709
  - effects on learning function 1984;63:729
  - effects on release of insulin in pancreatic islets 1981;60:878
  - electrocorticographic seizure activity 1975;54:722
  - electrographic and behavioral effects (abstract) 1980;59:527
  - epinephrine 1976;55:709
  - extrahepatic biotransformation 1981;60:129
  - failure in altering renal responses to acute intracranial pressure increases 1978;57:200
  - feedback control of delivery 1983;62:836
  - flammability 1975;54:238
  - for surgical removal of pheochromocytoma 1977;56:62
  - gastric fluid volume after 1980;59:287
  - halothane and absence of autoregulation of cerebral blood flow during anesthesia 1976;55:100
  - halothane and, protect against bronchospasm in asthma dog model 1978;57:629
  - halothane metabolite binding in obesity 1981;60:548
  - hematocrit effects on blood-gas solubility 1984;63:911
  - hepatic necrosis (abstract) 1982;61:172
  - hepatitis 1980;59:146
  - hepatitis following (letter) 1980;59:890
  - hepatotoxicity 1982;61:812, 1984;63:479, 1076
  - hepatotoxicity and surgical trauma 1982;61:79
  - ideal gases 1979;58:322
  - imbalance between CSF production and clearance (abstract) 1981;60:235
  - in obstetrics 1981;60:133
  - inhibition of 5-hydroxytryptamine removal 1982;61:671
  - inhibition of seizure activity during 1978;57:130
  - intrabiliary pressure changes in guinea pigs by narcotics 1979;58:120
  - intraocular pressure 1975;54:212
  - intraocular pressure during anesthesia in adult ophthalmic surgery 1980;59:50
  - intraoperative hypertension, patients with coronary artery disease (abstract) 1980;59:542
  - isoflurane and halothane comparative interaction of epinephrine in man 1976;55:709
  - isoflurane, fluroxene, methoxyflurane, and diethyl ether 1976;55:360
  - isoniazid effects (abstract) 1982;61:202
  - malignant hyperthermia 1975;54:47
  - measurement of anesthetic potency 1981;60:380
  - metabolic role of transplanted liver 1984;63:1131
  - metabolism at anesthetic and subanesthetic concentrations 1979;58:221
  - myocardial function during, coronary artery disease 1980;59:240
  - nitroprusside responses during 1979;58:174
  - nitrous oxide increases concentrations of, using vaporizers 1979;58:30
  - plasma catecholamine levels 1982;61:366
  - possible hazard with use of Ohio Ethrane vaporizer 1980;59:65
  - psychological functioning after 1980;59:245
  - relationship of EEG abnormalities to 1977;56:509
  - reproductive toxicity of 1982;61:19
  - responses to verapamil and (abstract) 1982;61:193
  - safety, following administration of aminophylline 1981;60:871
  - seizures in patients taking amitriptyline 1982;61:67
  - serum inorganic fluoride levels in obese patients 1979;58:409
  - thermoregulatory defect in rats during anesthesia 1977;56:09

- **Anesthetics, volatile**—*continued*
  - enflurane—*continued*
    - treatment of increased PCWP (abstract) 1981;60:273
    - uterine contractility in rabbits and 1978;57:160
    - vaporizer accuracy with nitrous oxide (letters) 1979;58:440, 441
    - ventilatory and cardiovascular effects during spontaneous ventilation 1978;57:610
    - ventilatory depression by, during clinical anesthesia 1980;59:103
    - ventricular arrhythmias following epinephrine injection 1975;54:468
  - ether, diethyl, hepatocyte responses, changes in surface scanning and enzyme leakage 1978;57:605
  - ether, diethyl, effects on muscle contractility 1984;63:451
  - flurothyl, convulsant gases and anesthetics 1981;60:464
  - fluroxene
    - for jejunoileal shunt 1975;54:65
    - gas machine hazards 1976;55:26
    - ouabain tolerance 1976;55:360
    - toxicity, chemical report 1976;55:529
  - halothane 1984;63:1059
    - a neurochemical hypothesis 1975;54:242
    - (abstract) 1984;63:191, 233, 248, 276
    - acetate fails to reverse myocardial depression in dogs anesthetized with 1978;57:395
    - adrenergic arrhythmias after imipramine 1984;63:825
    - age and epinephrine-induced arrhythmias (abstract) 1981;60:254
    - age-dependent responses to 1981;60:182
    - alcohol influence on 1980;59:826
    - alteration in heated humidifiers (letter) 1980;59:518
    - aminophylline pharmacokinetic and cardiorespiratory effects 1980;59:186
    - and enflurane, protect against bronchospasm in asthma dog model 1978;57:629
    - and halothane-nitrous oxide, neutrophil chemotaxis during 1977;56:696
    - and pentobarbital, effect on dispersion of indicator particles in central circulation of dog 1977;56:68
    - anesthesia and hemorrhage 1981;60:481
    - anesthetics and murine intelligence 1981;60:794
    - arrhythmias, dogs 1982;61:414
    - arrhythmogenic effects of aminophylline, experimental animals 1980;59:410
    - baroreceptor reflexes and pulmonary hemodynamics in the pig 1981;60:701
    - BAX-3224, comparison 1975;54:144
    - behavioral consequences, rats 1975;54:628
    - biotransformation and hepatic binding of metabolites (abstract) 1981;60:279
    - blood solubility during cardiopulmonary bypass, with crystalloid hemodilution and hypothermia 1977;56:622
    - calcium transport by cardiac sarcoplasmic reticulum 1981;60:390
    - canine ventricular cardiac conduction 1980;59:327
    - carcinogenicity of, in mice 1978;57:678
    - cardiac arrhythmias following aminophylline in experimental animals 1981;60:517
    - cardiovascular depression in infants 1982;61:42
    - cardiovascular effects 1976;55:85
    - cardiovascular effects, patients with coronary artery disease (abstract) 1980;59:536
    - cardiovascular responses to asphyxial challenge in chronically hyperkalemic dogs 1983;62:991
    - cardiovascular responses to nitrous oxide during anesthesia 1978;57:84
    - changes in neuronal activity, nucleus reticularis gigantocellularis 1980;59:897
    - circulatory effects compared with isoflurane 1984;63:635
    - clonidine reduction of halothane MAC 1982;61:741
    - comparative study using systolic time intervals 1976;55:263
    - comparison with isoflurane for CABG 1983;62:15
    - comparison with large single-dose fentanyl 1982;61:521
    - comparison with myocardial depressant action of thiopental 1984;63:313
    - complications in children 1984;63:838
    - concentrations during gastric or gallbladder traction, circulatory responses 1976;55:388
    - COPD and respiratory complications 1983;62:975
    - cyclopropane and, effect of dextroamphetamine and reserpine 1975;54:655
    - debromination prediction 1979;58:470
    - defect in muscle of hyperthermia-susceptible pig 1980;59:250
    - depression of lung mucociliary clearance by 1979;58:387
    - digital and sampled-data control of arterial blood pressure 1982;61:1010
    - drug therapy of ischemic myocardium 1982;61:10
    - echocardiographic analysis of cardiac performance 1979;58:23
    - effect of intrauterine exposure on postnatal autotolerance and brain weight 1983;62:565
    - effect of isoproterenol and propranolol 1976;55:383
    - effect of ketamine, on cardiovascular dynamics 1975;54:588
    - effect of levodopa 1975;54:178
    - effect of pancuronium 1979;58:497
    - effect of spontaneous vs controlled ventilation on alveolar concentration in dogs 1977;56:32
    - effect of subanesthetic concentrations on behavior 1978;57:434
    - effect of sufentanil on MAC 1983;62:987
    - effect on beta-adrenergic receptors in canine myocardium 1981;60:401
    - effect on canine intracardiac impulse conduction during sinus rhythm, antiarrythmic anesthetic action 1977;56:187
    - effect on cardiac output and regional flow 1983;62:489
    - effect on isometric twitch and tetanus response 1975;54:527
    - effect on pulmonary antibacterial defense mechanisms 1979;58:505
    - effect on regional blood flow and cardiac output in the fetal lamb in utero (abstract) 1981;60:241
    - effect on systolic time intervals 1977;56:522
    - effect on temperature gradients in cardiac surgical patients 1983;62:1002
    - effect on the rate of CSF production 1983;62:581
    - effect on tracheal cilia 1980;59:426
    - effects in anemia 1979;58:195
    - effects of brain sodium, potassium, and osmolality on MAC 1978;57:404
    - effects of deuteration on potency 1984;63:495
    - effects of isoflurane on induced hepatic injury 1984;63:888
    - effects on blood pressure 1984;63:482
    - effects on brainstem auditory evoked potentials 1982;61:338
    - effects on central sympathetic and vagal tone 1983;62:129
    - effects on conductivity of AV node and His-Purkinje system in dog 1977;56:378
    - effects on drug metabolism 1984;63:709
    - effects on electrically stimulated atrial arrhythmias in digitalized dogs 1981;60:302
    - effects on enzyme system, platelets 1980;59:856
    - effects on regional blood flow

1984;63:557
electroencephalographic abnormalities following 1978;57:244
electrographic and behavioral effects in cat (abstract) 1980;59:527
enflurane and 1975;54:588
enflurane and, absence of autoregulation of cerebral blood flow during anesthesia 1976;55:100
enflurane and isoflurane, comparative interaction of epinephrine in man 1976;55:709
enzyme induction following surgery 1981;60:319
epinephrine 1976;55:709
epinephrine, arrhythmogenic dose (abstract) 1981;60:258
epinephrine-induced arrhythmias effect of exogenous prostaglandins and prostaglandin synthesis inhibition 1979;58:401
exposure 1975;54:449
exposure, behavioral consequences 1975;54:628
extrahepatic biotransformation 1981;60:129
failure of naloxone and naltrexone to antagonize in the dog 1979;58:36
failure to alleviate carcinoid syndrome 1980;59:621
fatal hepatic necrosis after, with juvenile rheumatoid arthritis 1977;56:589
fetal anesthetic requirement 1983;62:09
flammability 1975;54:238
gastric fluid volume after 1980;59:287
gastric traction, circulatory responses 1976;55:388
halothane–epinephrine arrhythmias 1984;63:297
halothane-induced depression of myocardial contractility 1984;63:285
halothane-induced hepatotoxicity (letter) 1983;62:540
hematocrit effects on blood-gas solubility 1984;63:911
hemodynamic effects 1976;55:135
hemodynamic effects in pediatrics 1984;63:731
hemodynamic interactions with verapamil 1984;63:791
hemodynamic responses to nifedipine during anesthesia 1983;62:903
hepatic blood flow and hepatic injury (abstract) 1981;60:253
hepatic blood flow and hypoxia (letter) 1981;60:769
hepatic blood flow in phenobarbital-pretreated rats 1981;60:306
hepatic injury 1982;61:824
hepatic lesions, following multiple exposures 1975;54:332
hepatocyte responses, changes in surface scanning and enzyme leakage 1978;57:605
hepatoprotective effect of oxygen and 1978;57:481
hepatotoxicity 1982;61:809, 812, 1984;63:479, 1076
hepatotoxicity and surgical trauma 1982;61:79
hypoxia and hepatotoxicity (letter) 1983;62:859
ideal gases 1979;58:322
impairment of tracheal ring ciliary activity 1979;58:500
increasing concentrations reduce nitroprusside requirement 1978;57:457
increasing myocardial oxygen demand 1983;62:788
inhibition of 5-hydroxytryptamine removal 1982;61:671
inhibition of during calcium uptake by isolated sarcoplasmic reticulum 1981;60:492
inhibitory effect of isoflurane 1984;63:399
interaction with antibiotics on isometric contractions on rat-heart muscle 1977;56:515
interaction with naloxone in longitudinal muscle of guinea pig ileum 1979;58:93
intrabiliary pressure changes in guinea pigs by narcotics 1979;58:120
intraoperative hypertension, patients with coronary artery disease (abstract) 1980;59:542
isometric twitch and tetanus response 1976;55:383
ischemic heart disease (abstract) 1982;61:170
isoflurane and, cardiovascular effects 1975;54:701
(letter) 1984;63:371
MAC, effect of cocaine administration 1975;54:422
MAC, effect of isoproterenol and propranolol in dogs 1976;55:383
MAC, phenobarbital in dogs 1976;55:677
MAC in fetus (abstract) 1981;60:249
maternal and neonatal effects for cesarean delivery 1983;62:516
measurement by ultraviolet spectroscopy 1980;59:481
measurement of anesthetic potency 1981;60:380
mechanical hyperventilation 1980;59:839
mechanical hyperventilation and atrial arrhythmias (abstract) 1980;59:526
metabolite and subsequent halothane exposures, hepatic pathology 1976;55:235
metabolite binding in obesity 1981;60:548
minimum alveolar concentrations in swine 1984;63:529
mutagenicity (letter) 1979;58:64
myocardial damage in coronary-artery bypass with 1977;56:556
myocardial depression, asynergic contraction 1980;59:178
myocardial function during, coronary artery disease 1980;59:240
myocardial oxygen consumption 1982;61:979
myocardial oxygen consumption, afterload changes in dogs 1980;59:233
negative inotropic effect in rabbit papillary muscle 1982;61:403
negative inotropic effects (abstract) 1983;62:273
neurochemical hypothesis 1975;54:242
nifedipine interaction, hemodynamic depression (abstract) 1982;61:218
nitrous oxide modification of renal function altered by 1977;56:690
oxygen availability and hepatotoxicity 1984;63:965
phenobarbital 1976;55:677
platelet dysfunction (abstract) 1982;61:217
psychological functioning after 1980;59:245
renal blood flow autoregulation and, compared with methoxyflurane or alphaprodine 1978;57:389
renal function, stress response 1981;60:552, (abstract) 1981;60:260
requirement for, and physostigmine 1978;57:180
residual, exposure 1975;54:449
right coronary circulation (abstract) 1980;59:559
subsequent exposures in animals sensitized to a halothane metabolite 1976;55:235
succinylcholine and, massive myglobinuria 1976;55:680
suppression of cell-mediated immunity 1980;59:666
thermoregulatory defect in rats during anesthesia 1977;56:09
uptake and distribution in infants 1983;62:404
uptake and pharmacokinetics 1983;62:733
vagosympathetic effects on the His-Purkinje system (abstract) 1983;62:268
ventricular arrhythmias, following epinephrine injection 1975;54:468
hepatic injury, induced by volatile anesthetics 1983;62:140, 146, 155
isoflurane 1983;62:100
(abstract) 1984;63:187, 245, 249, 252, 278

- **Anesthetics, volatile**—*continued*
  - isoflurane—*continued*
    - and pressure antagonism in mice 1977;56:97
    - anesthesia and hemorrhage 1981;60:481
    - anesthetic for the eighties 1981;60:666
    - aortic stenosis (abstract) 1982;61:206
    - bactericidal effects 1979;58:136
    - calcium transport, sarcoplasmic reticulum 1982;61:142
    - calibration of the Narkotest gas monitor (brief reports) 1976;55:441
    - carcinogenicity of 1978;57:678
    - cardiovascular effects after fentanyl (abstract) 1983;62:252
    - cardiovascular effects in infants 1983;62:411
    - cardiovascular effects of hypotension for cerebral aneurysm surgery 1983;62:742
    - cerebral aneurysm surgery (abstract) 1982;61:197
    - circulatory effects compared with halothane 1984;63:635
    - comparison with halothane for CABG 1983;62:15
    - convulsant gases and anesthetics 1981;60:46
    - COPD and respiratory complications 1983;62:975
    - discoloration and impurities (letter) 1983;62:366
    - effect of aminophylline on arrhythmogenicity 1983;62:568
    - effect on oxidative metabolism of halothane 1984;63:399
    - effect with or without 50% nitrous oxide 1983;62:499
    - effects of halothane-induced hepatic injury 1984;63:888
    - effects on drug metabolism 1984;63:709
    - effects on hepatic dysfunction 1984;63:775
    - effects on regional blood flow 1984;63:557
    - epinephrine 1976;55:709
    - evaluation of a vaporizer 1982;61:457
    - fentanyl–nitroprusside for patients with cardiac valvular insufficiency (abstract) 1983;62:277
    - flammability 1975;54:238
    - for pheochromocytoma 1975;54:419
    - for resection of pheochromocytomas (letter) 1983;62:955
    - halothane and, cardiovascular effects, elderly patients 1975;54:701
    - halothane and, coronary artery disease, hemodynamics 1976;55:135
    - hematocrit effects on blood-gas solubility 1984;63:911
    - hemodynamic responses during hypotension (abstract) 1983;62:261
    - hepatic metabolism of 1984;63:805
    - hepatic necrosis (abstract) 1982;61:172
    - hepatotoxicity 1984;63:479, 1076
    - hepatotoxicity and surgical trauma 1982;61:79
    - hypertension 1975;54:419
    - hyperthermia (letters) 1982;61:711, 712
    - ideal gases 1979;58:322
    - inhalational anesthesia for coronary revascularization (letter) 1983;62:1047
    - inhibition of 5-hydroxytryptamine removal 1982;61:671
    - ischemic heart disease (abstract) 1982;61:170
    - liver toxicity, rats 1982;61:812
    - maternal and neonatal effects for cesarean delivery 1983;62:516
    - measurement of anesthetic potency 1981;60:380
    - minimum anesthetic concentration in children 1984;63:418
    - ouabain tolerance 1976;55:330
    - oxygen availability and hepatotoxicity 1984;63:965
    - pheochromocytoma 1975;54:419
    - platelet dysfunction (abstract) 1983;62:286
    - respiratory complications in COPD (abstract) 1983;62:263
    - responses to verapamil and (abstract) 1982;61:193
    - thermoregulatory defect in rats during anesthesia 1977;56:09
  - isoflurane requirement, effect of acute and chronic ethanol administration 1975;54:277
  - iso-Indoklon, convulsant gases and anesthetics 1981;60:464
  - methoxyflurane
    - bactericidal effects 1979;58:136
    - biotransformation and renal function 1976;55:415
    - carcinogenicity of 1978;57:678
    - dependence on cytochrome P-450 1982;61:609
    - developmental toxicity 1980;59:421
    - effect on ventricular automaticity, antiarrhythmic anesthetic action 1977;56:194
    - fluoride levels following analgesia, in parturients and neonates 1977;56:646
    - hematocrit effects on blood-gas solubility 1984;63:911
    - hepatocyte responses, changes in surface scanning and enzyme leakage 1978;57:605
    - metabolism at anesthetic and subanesthetic concentrations 1979;58:221
    - of trace concentrations 1978;57:328
    - ouabain tolerance 1976;55:360
    - renal blood flow autoregulation and, compared with halothane or alphaprodine in dog 1978;57:389
    - self-administered by parturients, medicolegal aspects (questions and answers) 1977;56:322
    - sevoflurane 1975;54:829
    - thermoregulatory defect in rats during anesthesia 1977;56:09
  - pharmacokinetics 1982;61:587
  - pneumothorax after laparoscopy 1983;62:1121
  - sevoflurane 1975;54:758
  - sevoflurane and methoxyflurane, enzyme induced 1975;54:829
  - sevoflurane, biotransformation of 1981;60:186
  - solubility in blood, estimation of (brief reports) 1976;55:593, thermoregulatory defect in rats during anesthesia 1977;56:09
  - thiomethoxyflurane, inhaled, characteristics of 1977;56:387
  - trace concentrations
    - cause for concern 55 years ago (correspondence) 1978;57:516
    - effect on behavior 1978;57:434
    - effect on infants of operating room personnel 1979;58:302
    - faulty anesthesia circuits, source of pollution 1977;56:359
    - in sperm (abstract) 1981;60:281
    - mechanical aspects of pollution control 1977;56:769
    - monitoring occupational exposure 1977;56:778
    - operating room pollution, governmental perspectives and guidelines 1977;56:775
    - psychomotor performance after exposure to 1979;58:475
  - trichloroethylene, self-administered by parturients, medicolegal aspects (questions and answers) 1977;56:322
  - uptake and pharmacokinetics 1983;62:733
- **Angioneurotic edema,** see Complications
- **Angiotensin,** see Polypeptides
- **Ankle block,** see Anesthetic techniques, regional
- **Anoxia,** see
  - Brain
  - Hypoxia
- **Antacids,** see Gastrointestinal tract, stomach
- **Antagonists, miscellaneous**
  - diazepam reversal of physostigmine (letter) 1980;59:805
  - doxapram, respiratory depression 1975;54:352
  - physostigmine
    - antagonizes ketamine 1980;59:764
    - –atropine solution, failure to reverse diazepam sedation 1980;59:58
    - failure to reverse effects of lorazepam

    1983;62:679
    hemodynamic responses in patients with a drug overdose 1983;62:885
    pressor response (letter) 1980;59:517
    reversal of datura stramonium delirium (brief reports) 1975;54:158
    reversal of diazepam-induced depression 1977;56:348
    reversal of lorazepam delirium 1975;54:607
    reversal of sedation in parturients 1976;55:478

**Antagonists, narcotic**
  nalbuphine
    adjunct to general anesthesia (letter) 1981;60:168
    premedication with 1977;56:808
  naloxone
    antagonism after narcotic supplemented anesthesia 1976;55:800
    cardiovascular response during enflurane anesthesia (abstract) 1981;60:237
    catecholamine blood levels 1982;61:349
    common bile duct pressure changes 1984;63:441
    effect on lidocaine analgesia in mice 1979;58:85
    effects on hemodynamics and plasma catecholamine 1983;62:305
    fails to antagonize thiopental 1978;57:558
    failure to antagonize halothane anesthesia in the dog 1979;58:36
    failure to reverse analgesia from transcutaneous electrical stimulation 1981;60:81
    hydroxyzine-naloxone interaction 1981;60:634
    hypertension and atrial premature contractions 1979;58:524
    hypertension (letter) 1980;59:806
    interaction with halothane in longitudinal muscle of guinea pig ileum 1979;58:93
    intravenous, hemodynamic and catecholamine responses to (abstract) 1982;61:182
    pressor response (letter) 1980;59:517
    rational use of (letter) 1981;60:120
    reversal of morphine-induced biliary colic 1980;59:619
    sudden death following 1980;59:782
  naltrexone, failure to antagonize halothane anesthesia in the dog 1979;58:36
  pH dependence in clinical anesthesia 1976;55:253

**Antagonists, neuromuscular relaxants**
  4-aminopyridine 1980;59:678
    and human electroencephalograph 1982;61:354
    neostigmine and, antagonism of lincomycin-pancuronium blockade with 1978;57:316
  amitriptyline therapy increases electrocardiographic changes during blockade reversal 1978;57:77
  anticholinesterase drugs, beta-adrenergic blockade and 1982;61:153
  atropine and neostigmine, esophageal sphincter tone during blockade reversal by 1978;57:171
  edrophonium
    100-hertz tetanus and train-of-four 1982;61:439
    effect on twitch depression and train-of-four ratio 1983;62:314
    heart rate following (abstract) 1982;61:167
    optimal dose for the reversal of norcuron (abstract) 1983;62:271
    train-of-four-fade of neuromuscular block, by succinylcholine in man 1976;55:663
  neostigmine 1980;59:678
    4-aminopyridine and, antagonism of lincomycin-pancuronium blockade with 1978;57:316
    cardiac dysrhythmia following, in geriatric patients 1978;57:186
    comparison of glycopyrrolate and atropine during reversal of nondepolarizing neuromuscular block with 1977;56:182
    correlation with anticurare activity of tetanic stimulation 1981;60:175
    dose-response for anesthetized pediatric patients (abstract) 1983;62:259
    *d*-tubocurarine, pancuronium, and polymyxin B, interaction on neuromuscular function 1976;54:224
    effect on intestine (questions and answers) 1977;56:594
    effect on twitch depression and train-of-four ratio 1983;62:314
    rational use of (letter) 1981;60:120
    reversal of blockade with atropine and glycopyrrolate 1981;60:557
    reversal of combination nondepolarized neuromuscular block 1983;62:1081
  Org NC 45, antagonism by neostigmine, pyridostigmine, 4-aminopyridine 1980;59:31
  physostigmine
    cardiac dysrhythmia following, in geriatric patients 1978;57:186
    halothane requirement in dogs and 1978;57:180
    lorazepam delirium 1975;54:607
    reversal of halothane (correspondence) 1978;57:597, 598
  pre- and postjunctional effects (letter) 1983;62:1137
  pyridostigmine 1975;54:317
  pyridostigmine, effect on twitch depression and train-of-four ratio 1983;62:314

**Antibiotics**
  aminoglycoside, neuromuscular blocking effects 1976;55:500
  cefazolin, neuromuscular blocking effects 1982;61:767
  cephalosporin, hepatitis (letter) 1980;59:806
  cephalothin, failure to produce anaphylaxis 1980;59:393
  cephapirin, anaphylactic reaction during spinal anesthesia 1979;58:337
  chloramphenicol, interaction with halothane on isometric contractions on rat-heart muscle 1977;56:515
  clindamycin, and lincomycin, comparative neuromuscular effects 1977;56:329
  gentamicin
    neuromuscular blocking effects 1982;61:767
    pancuronium interaction, renal failure (letter) 1980;59:393
  interaction with muscle relaxants, neuromuscular effects 1979;58:107
  kanamycin, interaction with halothane on isometric contractions on rat-heart muscle 1977;56:515
  lincomycin
    and clindamycin, comparative neuromuscular effects 1977;56:329
    neuromuscular blockade with pancuronium, antagonism with neostigmine and 4-aminopyridine 1978;57:316
  lincomycin-curare interaction 1975;54:103
  muscle relaxants potentiated 1976;55:224
  neuromuscular drug interactions 1980;59:678
  neuromuscular junction, interaction with muscle relaxants 1979;58:107
  penicillin, neuropathy (letter) 1979;58:63
  polymyxin B, *d*-tubocurarine, pancuronium, and neostigmine, interaction on neuromuscular function 1976;55:224
  polymyxin B, neuromuscular block by 1977;56:373
  prolonged epidural catheterization (questions and answers) 1976;55:132
  streptomycin, interaction with halothane on isometric contractions on rat-heart muscle 1977;56:515
  tobramycin
    interaction with curare 1977;56:587
    neuromuscular blocking effects of 1982;61:200
    neuromuscular blocking effects of (abstract) 1982;61:767

**Antibiotics**—*continued*
- vancomycin, anaphylactoid reaction to, during anesthesia 1977;56:870

**Anticonvulsants**
- benzodiazepines, protect mice from local anesthetic convulsions and death 1981;60:385
- diazepam, catecholamine release with morphine 1981;60:406
- ketamine, suppression of chemically induced convulsions in infant cockerel 1980;59:406
- phenytoin, cardiac protection in hypoxia 1984;63:1021

**Antidepressants,** see Ataractics

**Antidiuretic hormone,** see Hormones

**Antiemetics,** see Vomiting

**Apnea,** see Ventilation

**Arrest, cardiac,** see
- Complications
- Heart, massage

**Arrhythmia,** see Heart

**Arterial blood-gas analyses**
- during electroconvulsive therapy in a parturient 1975;54:203

**Arteries**
- Allen's test, the case for a complete Allen's test 1983;62:947
- arteritis, Takayasu, anesthetic considerations 1979;58:247
- axillary, localizing (letter) 1983;62:701
- cannulation
  - Doppler-assisted 1984;63:346
  - hand ischemia 1982;61:465
  - occlusion 1975;54:836
  - peroneal artery in adults 1981;60:360
  - safety 1979;58:256
- carotid
  - inadvertent prolonged cannulation 1982;61:150
  - puncture, internal jugular cannulation (abstract) 1982;61:181
- cerebral, direct effects of ketamine 1983;62:553
- coronary
  - circulatory changes following the amylal succinylcholine and tracheal intubation 1976;55:232
  - fentanyl 1981;60:21
  - insufficiency, nitrous oxide 1984;63:1071
  - myocardial infarction 1983;62:493
  - preoperative prophylactic digitalis 1983;62:865
- dorsalis pedis, blood pressure in great toe with simulated occlusion 1978;57:453
- function, analysis of cardiovascular regulation 1977;56:761
- local anesthetics, vascular smooth muscle, rabbit 1982;61:756
- Mönckeberg's arteriosclerosis, pseudohypertension due to 1978;57:588
- radial
  - cannulation 1982;61:876
  - cannulation (letter) 1983;62:540
  - catheterization, ischemic injury following 1979;58:55
  - median nerve compression following puncture 1980;59:953
  - puncture simulator 1978;57:733
  - safety of percutaneous arterial cannulation 1979;58:256
- trimethaphan, α-adrenoceptor antagonist 1984;63:290

**ASA classification** (questions and answers) 1976;55:614

**Aspiration,** see
- Complications
- Lung

**Asthma,** see Lung

**Asystole,** see
- Complications
- arrest, cardiac
- Heart

**Ataractics**
- abuse, by anesthesia personnel 1983;62:467
- antidepressants
  - amitriptyline 1982;61:67
  - doxepin, chronic pain, depression and serum opioids (abstract) 1982;61:187
  - tricyclic and chronic pain 1984;63:1025
- benzquinamide, cardiovascular effects 1979;58:189
- cannabinol, dental surgery, cardiovascular effects 1976;55:203
- droperidol and diazepam, changes in airway resistance 1976;55:18
- droperidol, effectiveness of hydroxyzine compared with droperidol 1981;60:783
- hydroxyzine
  - comparison with droperidol and diazepam as premedication 1977;56:496
  - effect on morphine analgesia 1980;59:690
  - compared with droperidol 1981 60:783
  - respiratory depression 1981;60:634
- imipramine, halothane–epinephrine induced arrhythmias 1984;63:825
- MAO inhibitors and anesthesia for cardiac surgery 1984;63:1041
- phenothiazines, promethazine, neonatal electroencephalographic patterns as affected by maternal administration 1978;57:303
- promethazine, and morphine, as premedicants 1977;56:801
- rauwolfia, reserpine, treatment of reflex sympathetic dystrophy 1980;59:500
- reserpine (letters) 1980;59:889
- tricyclic antidepressants, amitriptyline therapy increases electrocardiographic changes during neuromuscular blockade reversal 1978;57:77
- tricyclic antidepressants (letter) 1984;63:1140

**Atelectasis,** see
- Complications
- Lung

**Atracurium,** see Neuromuscular relaxants

**Atropine,** see
- Parasympathetic nervous system
- Premedication

**Auditing,** see Anesthesiology

**Awareness,** see
- Anesthesia, depth
- Memory

**Axillary block,** see Anesthetic techniques, regional

**Bacteremia,** see Infection

**Bacteria**
- contamination, in heated nebulizers 1978;57:191
- epidural analgesia, bacteriologic aspects 1976;55:187
- humidifiers, heated, contaminants in 1978;57:191

**β-Adrenergic receptors,** see Sympathetic nervous system

**Bags, ventilation anesthesia,** see Equipment, breathing bags

**Bain system,** see Equipment, circuits

**Balanced anesthesia,** see Anesthetic techniques, balanced

**Barbital,** see Hypnotics, barbiturates

**Barbiturates,** see Hypnotics

**Baroreceptors,** see
- Receptors, presso-
- Reflexes

**Bartter's syndrome,** see Complications

**Benzodiazepines,** see Hypnotics

**Benzquinamide,** see
- Ataractics
- Vomiting, antiemetics

**Bicarbonate,** see Acid-base equilibrium

**Biliary tract,** see Liver

**Binding,** see
- Protein
- Receptors

**Biotransformation (drug)**
- age factors, pharmacokinetics of fentanyl 1982;61:968
- assay techniques
  - limitations of sodium fusion assay 1982;61:786
  - pseudocholinesterase atypical 1976;55:243
- cocaine
  - succinylcholine sensitivity 1979;58:235
- enflurane, at anesthetic and subanesthetic concentrations 1979;58:221
  - fluoride levels in obese patients 1979;58:409
  - metabolic role of transplanted liver 1984;63:1131

- enzyme induction
  - extrahepatic biotransformation of halothane and enflurane 1981;60:129
  - following surgery with halothane and neurolept anesthesia 1981;60:319
  - hepatotoxicity and surgical trauma 1982;61:79
- fluorinated metabolites, detection by sodium fusion 1980;59:62
- fluorometabolites, halothane and metabolite binding in obesity 1981;60:548
- halothane 1982;61:824
  - debromination prediction 1979;58:470
  - inhibitory effect of isoflurane 1984;63:399
- isoflurane, hepatic metabolism of 1984;63:805
- methoxyflurane
  - at anesthetic and subanesthetic concentrations 1979;58:221
  - dependence on cytochrome P-450 1982;61:609
- microsomes, extrahepatic biotransformation of halothane and enflurane 1981;60:129
- pancuronium, antagonism by neostigmine 1979;58:483
- sevoflurane, toxologic changes 1981;60:186
- volatile anesthetics and drug metabolism 1984;63:709

**Bisulfite,** see Pharmacology, preservatives

**Bladder,** see Surgery, urologic

**Bleomycin,** see Toxicity

**Blindness,** see
- Complications
- Eye

**Block,** see
- Anesthetic techniques, regional
- Heart

**Blood**
- anemia
  - hemodynamic effects of halothane 1979;58:195
  - transfusion complication 1979;58:439
- anticoagulants
  - heparin, and antagonism during cardiopulmonary bypass with hypothermia 1977;56:564
  - heparin, cardiopulmonary bypass (abstract) 1982;61:189
- arterial and venous plasma levels of bupivacaine following peripheral nerve blocks 1976;55:763
- bleeding diathesis of uncertain origin, anesthetic considerations 1976;55:173
- carboxyhemoglobin, elevated intraoperative levels (letter) 1984;63:698
- coagulation
  - anticoagulants and continuous epidural anesthesia (letters) 1980;59:394
  - assessment and reversal of heparin-induced anticoagulation for cardiopulmonary bypass 1983;62:710
  - cardiovascular effects of protamine 1981;60:33
  - effect of protamine on hypoxic pulmonary vasoconstriction in dogs (abstract) 1981;60:259
  - halothane effects 1980;59:856
  - hemodynamic effects 1983;62:831
  - hemophilia, hypotension associated with acute abdomen 1976;55:346
  - heparin 1983;62:1095, (abstract) 1984;63:235
  - heparin, contamination in studies from indwelling lines 1980;59:222
  - heparin, effects on ischemic brain injuries 1976;55:683
  - (letter) 1984;63:783, 1143
  - management of hemophiliac patients 1979;58:133
  - platelet involvement in heparinized blood 1984;63:394
  - procedures necessitated by massive hemorrhage during cardiopulmonary bypass 1978;57:273
  - protamine 1983;62:1095
  - protamine, calcium antagonism (abstract) 1980;59:564
  - protamine, effect on canine heart muscle 1980;59:100
  - protamine, myocardial metabolic effects, cardiopulmonary bypass (letter) 1982;61:476
  - protamine, severe circulatory shock following 1980;59:77
  - protamine sulfate and myocardial metabolism 1982;61:247
  - protamine toxicity in isolated heart tissue 1984;63:1111
  - rate of injection of protamine (letter) 1981;60:538
- cold agglutination 1984;63:349
- dextran-local anesthetic interactions 1980;59:335
- filters
  - respiratory failure (abstract) 1980;59:539
  - transfusion, evaluation of 1978;57:463
- flow distribution, with induced hypotension 1984;63:503
- glucose, perioperative hypoglycemia 1983;62:1035
- hematocrit, effects on blood-gas solubility 1984;63:911
- hematology, diffuse bleeding, diathesis of uncertain origin 1976;55:173
- hemodilution effect on hypotension, cardiopulmonary bypass 1975;54:482
- hemoglobin
  - degradation, induced hypotension 1980;59:197
  - enflurane blood-gas solubility 1982;61:1006
- heparin, protamine sulfate and myocardial metabolism 1982;61:247
- leukocytes
  - influence of spinal and epidural anesthesia on neutrophil chemotaxis 1978;57:567
  - neutrophil chemotaxis during halothane and halothane-nitrous oxide anesthesia 1977;56:696
  - neutrophil chemotaxis 1976;55:668
- loss, operative, total hip replacement 1975;54:641
- lymph, leakage following catheterization of right subclavian vein 1978;57:123
- mediastinal Hodgkin's disease, airway obstruction (case history) 1975;54:399
- methemoglobinemia, organic nitrate therapy and 1979;58:521
- oncotic pressure, serum and hydrostatic pressure differences in critically ill patients 1982;61:496
- perfluorocarbons, liquid-gas partition coefficients of halothane and isoflurane 1984;63:690
- pH dependence of narcotics and narcotic antagonists 1976;55:253
- phagocytosis during general anesthesia 1975;54:501
- plasma concentration after lidocaine endotracheal spray 1975;54:438
- plasma, in interstitial lung diseases 1979;58:13
- plasma levels, arterial and venous 1976;55:763
- plasma levels, diazepam 1975;54:173
- platelet, aggregation, general anesthesia and surgery 1979;58:293
- platelets, halothane effects 1980;59:856
- protamine, toxicity in isolated heart tissue 1984;63:1111
- intraoperative replacement (brief reports) 1975;54:550
- rheology, review 1978;57:252
- serum creatine phosphokinase, malignant hyperpyrexia 1976;55:797
- sickle cell disease, aortic and mitral valve replacement (letter) 1982;61:802
- sickle cell disease, dynamics of red blood cells, anesthesia 1975;54:361
- solubility (brief reports) 1976;55:593
- transfusion, cardiac failure, associated with hypocalcemia 1976;55:34
- treatment of acute loss with components 1975;54:01
- unrelenting hypotension, associated with an acute abdomen in a comatose hemophiliac child 1976;55:346
- use of $NaHCO_3$ in administration of bank blood (questions and answers) 1976;55:274

**Blood**—*continued*
  venous $P_{50}$, cardiac disease and anesthesia 1980;59:751
  volume
    expansion in interstitial lung diseases 1979;58:13
    mannitol, effects on blood volume and central hemodynamics during cerebral aneurysm surgery 1983;62:875
  volume determination usefulness preoperatively (questions and answers) 1976;55:275
  volume measurement preoperative (questions and answers) 1976;55:275
**Blood patch,** see Anesthetic techniques, epidural
**Blood pressure**
  acute hypotension during laparoscopy 1975;54:142
  arterial, effect of atropine 1975;54:262
  catheter positioning (brief reports) 1975;54:696
  internal jugular venipuncture (brief reports) 1975;54:157
  monitoring (brief reports) 1975;54:549
  cryptenamine, control of hypertension during cardiopulmonary bypass with 1978;57:54
  diazoxide, hyperglycemic coma following 1977;56:506
  hypertension
    due to Mönckeberg's arteriosclerosis 1978;57:588
    isoflurane and halothane for CABG 1983;62:15
    nitroglycerin therapy, pregnant ewes 1980;59:494
    plasma catecholamine levels during anesthesia 1982;61:366
    role of central noradrenergic mechanisms 1984;63:482
  hypertonic solutions, hypotension and respiratory distress 1979;58:42
  hypotension
    blood loss determination during 1980;59:203
    (letter) 1982;61:713
    nitroprusside induced, effect on renal function 1978;57:521
    supine hypotensive syndrome (brief reports) 1976;55:887
  intubation, hypertension 1980;59:367
  measurement
    infants (letter) 1982;61:956
    modification of cuff (letter) 1982;61:476
    pseudohypotension (letter) 1982;61:713
    packed red cell 1975;54:89
  perioperative, significance of hypotension 1984;63:647
  preoperative computed tomography and intracranial pressure 1982;61:430
  servo systems, control of during halothane anesthesia 1982;61:1010
  systemic vascular resistance
    cardiovascular effects of enflurane during controlled ventilation 1978;57:619
    effects of enflurane during spontaneous ventilation 1978;57:610
  see
    Anesthetic techniques, hypotensive
    Arteries
    Heart
    Measurement techniques
    Monitoring
**Book reviews**
  Abel EL. Marihuana 1981;60:367
  Abel FL, McCutcheon EP. Cardiovascular function principles and applications 1979;58:534
  Abouleish E. Pain control in obstetrics 1978;57:385
  Adams AP, Hahn CEW. Principles and practice of blood-gas analysis 1980;59:165
  Aldrete JA, Lowe HJ, Virtue RW. Low flow and closed system anesthesia 1979;58:352
  Aldrete JA, Stanley TH. Trends in intravenous anesthesia 1980;59:812
  Alifimoff JK. Principles and practice of blood-gas analysis 1984;63:627
  Allen GD. Dental anesthesia and analgesia 1980;59:228
  Alling CC III, Mahan PE (eds). Facial pain 1978;57:154
  American Medical Association Department of Drugs. AMA drug evaluations, fourth edition 1980;59:638
  Assmann DC, Hixon SJ, Kacmarek RM. Clinical simulations for respiratory care 1979;58:533
  Attia RR, Grogono AW. Practical anesthetic pharmacology 1979;58:162
  Barnett WM. Medical emergency manual, 3rd ed. 1984;63:471
  Baselt RC. Analytical procedures for therapeutic monitoring and emergency toxicology 1980;59:522
  Bastron RD, Deutsch S. Anesthesia and the kidney 1977;56:760
  Beasley JM, Jones SEF. A guide to paediatric anaesthesia 1981;60:231
  Bedord RF. Clinical frontiers in anesthesiology 1984;63:377
  Beers RF, Bassett EG. Mechanisms of pain and analgesic compounds 1980;59:82
  Beks JWF, Bosch DA, Brock M (eds). Intracranial pressure III 1977;56:758
  Berk JL, Sampliner JE. Handbook of critical care, second edition 1982;61:626
  Bevan DR. Renal function in anaesthesia and aurgery 1980;59:396
  Bhagat BD. Mode of action of autonomic drugs 1979;58:534
  Bircher N. Anesthesiology—problem-oriented patient management 1984;63:378
  Blake TM. The practice of electrocardiography 1982;61:549
  Blitt CD. Catheterization techniques for invasive cardiovascular monitoring 1982;61:806
  Blodgett D. Manual of pediatric respiratory care procedures 1983;62:373
  Blodgett D. Manual of respiratory care procedures 1983;62:373
  Bochner F, Carruthers G, Kampmann J, Steiner J. Handbook of clinical pharmacology 1978;57:753
  Bonica JJ, Liebeskind JC, Albe-Fessard DG. Advances in pain research and therapy 1980;59:165
  Bonica JJ, Liebeskind JC, Albe-Fessard DG. Pain—Association for Research in Nervous and Mental Disease, volume 58 1980;59:461
  Bonica JJ, Ventafridda V. International Symposium on Pain of Advanced Cancer—Advances in pain research and therapy 1979;58:445
  Borland LM. Textbook of pediatric emergency medicine 1984;63:472
  Bowman WC. Pharmacology of neuromuscular function 1983;62:463
  Bradbury M. The concept of a blood-brain barrier 1980;59:713
  Branthwaite MA. Anaesthesia for cardiac surgery and allied procedures, second edition 1981;60:233
  Brewis RAL. Lecture notes on respiratory disease, 2nd ed 1981;60:71
  Britt BA. International anesthesiology clinics, volume 17 1980;59:396
  Brodsky JB. Clinical aspects of oxygen: international anesthesiology clinics, volume 19, number 3, fall 1981 1982;61:71
  Bromage PR. Epidural analgesia 1979;58:261
  Brown BR. Anesthesia and the patient with liver disease 1981;60:772
  Brown BR. Anesthesia and the obese patient: contemporary anesthesia practice, volume 5 1982;61:310
  Brown BR. Anesthesia and the patient with heart disease 1980;59:894
  Brown BR. Anesthesia and the patient with endocrine disease 1981;60:365
  Brown BR. Fluid and blood therapy in anesthesia 1983;62:1053
  Brown BR. Outpatient anesthesia 1979;58:352
  Brown RC. Perchance to dream 1982;61:71

Brown SS, Mitchell FL, Young DS. Chemical diagnosis of disease 1981;60:365
Brown TCK, Fisk GC. Anaesthesia for children 1980;59:397
Bruce DL. Functional toxicity of anesthesia 1981;60:125
Bruner JMR. Handbook of blood pressure monitoring 1979;58:353
Budassi SA, Barder J, Kimmerle L, Eie KF. Cardiac arrest and CPR 1981;60:232
Bunker JP, Barnes BA, Mosteller F (eds). Costs, risks, and benefits of surgery 1978;57:152
Burri C, Ahnefeld FW. The caval catheter 1979;58:160
Campkin TV, Turner JM. Neurosurgical anaesthesia and intensive care 1981;60:170
Carroll J. Pediatric anesthesia, volume 1 1984;63:626
Chalon J, Ali M, Turndorf H, Fischgrund GK. Humidification of anesthetic gases 1981;60:772
Chu LSW, Yeh SDJ, Wood DD. Acupuncture manual, a western approach 1980;59:397
Chung DC. Anesthesia in patients with ischaemic heart disease 1983;62:1053
Churchill-Davidson HC. A practice of anesthesia 1979;58:163
Cohen EL, Van Dyke RA, Trudell JR. Metabolism of volatile anesthetics 1977;56:880
Cohen EN. Anesthetic exposure in the workplace 1980;59:713
Collins VJ. Principles of anesthesiology (2nd ed) 1977;56:172
Committee on Workshops of the American Association of Blood Banks. Hemotherapy in trauma and surgery 1980;59:461
Comroe JH Jr. Retrospectroscope: insights into medical discovery 1978;57:290
Conahan TJ III. Cardiac anesthesia 1982;61:720
Coran AG, Behrendt DM, Weintraub WH, Lee DC. Surgery of the neonate 1979;58:261
Cosmi EV. Obstetric anesthesia and perinatology 1981;60:773
Cottrell JE. Occupational hazards to operating room and recovery room personnel, International Anesthesiology Clinics, volume 19 1982;61:549
Cottrell JE, Turndorf H. Anesthesia and neurosurgery 1980;59:462
Cousins MJ, Bridenbaugh PO. Neural blockade in clinical anesthesia and management of pain 1981;60:232
Covino BG, Vassallo HG. Local anesthetics, mechanisms of action and clinical use 1980;59:715
Cowley RA, Trump BE. Pathophysiology of shock, anoxia, and ischemia 1982;61:719
Crawford JS. Obstetric analgesia and anaesthesia 1983;62:462
Crooks J, Stevenson IH. Drugs and the elderly 1980;59:521
Cuschieri A, Baker PR. Introduction to research in medical sciences 1977;56:879
Dal Santo G. Nonrespiratory functions of the lung and anesthesia 1978;57:383
DeJong RH. Local anesthetics (2nd ed) 1978;57:155
DeKornfeld TJ, Detmer MD. Medical examination review, volume 12—anesthesiology, 5th ed 1981;60:71
DeKornfeld TJ, Finch JS. Respiratory care case studies 1983;62:463
DeKornfeld TJ. Selected papers in respiratory therapy, second edition 1980;59:82
Dobkin AB. Development of new volatile inhalation anesthetics 1979;58:533
Domino KB. New pharmacologic vistas in anesthesia, contemporary anesthesia practice 1984;63:964
Domino KB. Principles and practice of pharmacology for anaesthetists 1984;63:1145
Drain CB, Shipley SB. The recovery room 1980;59:165
Dripps RD, Eckenhoff JE, Vandam LD. Introduction to anesthesia: the principles of safe practice 1983;62:864
Dripps RD, Eckenhoff JE, Vandam LD. Introduction to anesthesia: the principles of safe practice 1978;57:155
Dudley H. Presentation of original work in medicine and biology 1978;57:154
Dundee JW. Intravenous anesthetic agents, current topics in anaesthesia, volume 1 1980;59:227
Dunnhill RPH, Colvin MP, Crawley DE. Clinical and resuscitative data, second edition 1980;59:463
Eckenhoff JE. 1980 year book of anesthesia 1981;60:233
Eckenhoff JE. Controversy in anesthesiology 1980;59:316
Eckenhoff JE. 1978 yearbook of anesthesia 1979;58:69
Eckenhoff JE, Bart AJ, Brunner EA, Holley HS, Linde HW. 1979 year book of anesthesia 1980;59:319
Effron DM. Cardiopulmonary resuscitation CPR 1979;58:354
Eger EI. Isoflurane 1981;60:773
Ellis FR. Inherited disease and anaesthesia, volume 9 1982;61:165
Eriksson E. Illustrated handbook in local anaesthesia 1980;59:398
Farzan S. A concise handbook of respiratory diseases 1979;58:65
Finch JS, DeKornfeld TJ. Respiratory care case studies 1977;56:171
Fink BR. Molecular mechanisms of anesthesia: progress in anesthesiology, volume 2 1981;60:366
First National Congress of Anaesthesia and Intensive Care (abstracts) 1977;56:172
Fischer KJ. Der einfluss von anaesthetica auf die kontraktionsdynamik des herzens 1980;59:462
Fishbach DP, Fogdall RP. Coagulation: the essentials 1982;61:397
Fishman AP. Assessment of pulmonary function 1980;59:635
Fitzgerald RS, Gautier H, Lahiri S. The regulation of respiration during sleep and anesthesia 1979;58:65
Flaim SF, Zelis R. Calcium blockers—mechanisms of action and clinical applications 1983;62:542
Frey R, Safar P. Disaster medicine—types of events of disasters organization in various disaster situations, volume 1 1980;59:635
Geevarghese KP. Anesthesia for neurological surgery 1978;57:383
George RB, Light RW, Matthay RA. Chest medicine 1983;62:959
Gerson GR. Monitoring during anesthesia: international anesthesiology clinics, volume 19, number 11 1981;60:846
Gill W, Long WB. Shock trauma manual 1980;59:316
Gilman AG, Goodman LS, Gilman A. Goodman and Gilman's The pharmacological basis of therapeutics, sixth edition 1981;60:367
Goedhard WJA (ed). Non-invasive mechanical methods in cardiology and cardiovascular dynamics 1977;56:759
Goldberger E. A primer of water, electrolyte and acid-base syndromes, sixth edition 1980;59:398
Gordon E. A basis and practice of neuroanaesthesia, second edition 1982;61:550
Gordon RJ, Ravin MB, Daicoff GR. Cardiovascular physiology for anesthesiologists 1979;58:446
Gorsky BH, Gorsky SR. Introduction to medical hypnosis 1982;61:810
Gorsky BH. Pain: Origin and treatment 1982;61:72
Gothard JWW, Branthwaite MA. Anesthesia for thoracic surgery 1983;62:372

**Book reviews**—*continued*
- Graedon J. The people's pharmacy: a guide to prescription drugs, home remedies, and over the counter medications 1977;56:757
- Gravenstein JS, Newbower RS, Ream AK, Smith NT, Barden J. Monitoring surgical patients in the operating room 1979;58:261
- Gravenstein JS, Newbower RS, Smith NT. Essential noninvasive monitoring in anesthesia 1981;60:69
- Gray TC, Nunn JF, Utting JE. General anaesthesia, fourth edition, volumes 1 & 2 1980;59:636
- Greene NM. Key words in anesthesiology, second edition 1980;59:463
- Greene NM. Physiology of spinal anesthesia, third edition 1981;60:915
- Gregory GA. Respiratory failure in the child 1982;61:806
- Grenvik A, Safar P. Brain failure and resuscitation 1982;61:397
- Grodins FS, Yamashiro SM. Respiratory function of the lung and its control 1979;58:160
- Grundy BL, Gravenstein JS. Quality of care in anesthesia 1983;62:243
- Guenter CA, Welch MH. Pulmonary medicine 1982;61:958
- Guerra F, Aldrete JA. Emotional and psychological responses to anesthesia and surgery 1980;59:894
- Gupta RC. Epidurography: a diagnostic aid in spinal lesions 1979;58:353
- Halstead CL, Blozis GG, Drinnan AJ, Gier RE. Physical evaluation of the dental patient 1982;61:890
- Hamburg J (ed). Review of allied health education (vol 2) 1977;56:757
- Hanson GC, Wright PL. The medical management of the critically ill 1980;59:812
- Harcus AW, Smith R, Whittle B. Pain—new perspectives in measurement and management 1978;57:751
- Harlan BJ, Starr A, Harwin FM. Manual of cardiac surgery, volume I 1981;60:170
- Hendler N. Diagnosis and nonsurgical management of chronic pain 1981;60:620
- Henschel EO (ed). Malignant hyperthermia: current concepts 1978;57:153
- Hercules PR, Lekwart FJ, Fenton MV. Pulmonary restriction and obstruction, a programmed text 1980;59:896
- Hill DW. Physics applied to anesthesia, fourth edition 1981;60:172
- Hill DW. Physics applied to anaesthesia 1977;56:171
- Hoffman JF (ed). Membrane transport processes 1978;57:384
- Holdcroft A. Body temperature control 1981;60:366
- Howe JF. Patient care in neurosurgery 1977;56:881
- Israel JS, DeKornfeld TJ. Recovery room care 1982;61:719
- Ivankovich AD. Nitroprusside and other short-acting hypotensive agents 1979;58:66
- Jacox AK. Pain, a source book for nurses and other health care professionals 1977;56:879
- James FM, Wheeler AS. Obstetric anesthesia: the complicated patient 1982;61:626
- Johnstone RE. Anesthesiology continuing education review 1977;56:171
- Jones NL. Blood gases and acid-base physiology 1980;59:397
- Jorgenson NB. Hayden J, Sedation, local and general anesthesia in dentistry, third edition 1980;59:713
- Kaplan JA. Thoracic anesthesia 1983;62:543
- Kaplan JA. Cardiac anesthesia 1979;58:354
- Katz J, Benumof J, Kadis LB. Anesthesia and uncommon diseases: pathophysiology and clinical correlations, second edition 1981;60:915
- Katzung BG. Basic and clinical pharmacology 1983;62:784
- Kaufman L, Sumner E. Medical problems and the anaesthetist—current topics in anaesthesia, volume 4 1981;60:69
- Kennedy RL. Management of epidural analgesia in childbirth 1984;63:705
- Kharkevich DA. Pharmacology of ganglionic transmission, volume 53 1980;59:957
- Kilpatrick A. Practical dental anaesthesia 1980;59:714
- King LS. Why not say it clearly 1979;58:262
- Kirby RR, Graybar GB. International anesthesiology clinics, intermittent mandatory ventilation, volume 18, summer, 1980 1980;59:957
- Kitahata LM, Collins JG. Narcotic analgesics in anesthesiology 1982;61:480
- Klide AM, Kung SH. Veterinary acupuncture 1978;57:291
- Kline J. Biological foundations of biomedical engineering 1979;58:161
- Kruk ZL, Pycock CJ. Neurotransmitters and drugs 1980;59:521
- Leanza R. Problems with anesthetic and respiratory therapy equipment 1984;63:172
- Ledingham IM, MacKay C. Jamieson & MacKay's textbook of surgical physiology, third edition 1980;59:83
- Ledingham IMcA. Recent advances in intensive therapy 1979;58:66
- Lee JA, Atkinson RS. Sir Robert MacIntosh's lumbar puncture and spinal analgesia (intradural and extradural) 1979;58:355
- Lenhert BE, Schachter EN. The pharmacology of respiratory care 1980;59:895
- LeRoy PL (ed). Current concepts in the management of chronic pain "pro dolore" 1977;56:880
- Levin DL, Morriss FC, Moore GC. A practical guide to pediatric intensive care 1981;60:233
- Levin RM. Pediatric anaesthesia handbook 1981;60:172
- Levine RJ. Ethics and regulation of clinical research 1982;61:480
- Levitzky MG. Pulmonary physiology 1983;62:374
- Lipton S (ed). Persistent pain: modern methods of treatment 1978;57:156
- Lipton S. Relief of pain in the clinical practice 1980;59:637
- Lipton S. The control of chronic pain, current topics in anaesthesia, volume 2 1980;59:463
- Lipton S, Miles J. Persistent pain: modern methods of treatment, volume 3 1982;61:626
- Lisbon A. Anesthetic considerations in setting up a new medical facility: International Anesthesiology Clinics, summer, volume 19 1981;60:774
- List WF, Gravenstein JS, Spodick DH. Systolic time intervals 1980;59:895
- Liu PH. Cardiac arrhythmias 1984;63:884
- Loeschcke HH (ed). Acid–base homeostasis of the brain extracellular fluid and the respiratory control system 1977;56:760
- Lough MD, Doershuk CF, Stern RC. Pediatric respiratory therapy, second edition 1980;59:166
- Lough MD, Williams TJ, Rawson JE. Newborn respiratory care 1981;60:125
- Lowe HJ, Ernst EA. The quantitative practice of anesthesia use of closed circuit 1981;60:846
- Lunn JN. Lecture notes on anaesthetics 1979;58:535
- MacDonald AG, Wann KT. Physiological aspects of anaesthetics 1979;58:536
- MacDonnell KF, Segal MS (eds). Current respiratory care 1977;56:881
- Mackenzie CF, Ciesla N, Imle PC, Klemic N. Chest physiology in the

intensive care unit 1982;61:481
Malik AB, Staub NC. Mechanisms of lung microvascular injury (volume 384) 1983;62:462
Mallory GB. Control of respiration 1984;63:627
Mallory GB. Pulmonary function testing guidelines and controversies 1984;63:707
Margand PMS, Brooks CG, Hunter JW. Preoperative pulmonary preparation 1981;60:698
Markello R. Anesthesiology and the law 1984;63:708
Markello R. Complications in anesthesiology 1984;63:95
Markello R. Mortality in anesthesia (Proceedings of the European Academy of Anaesthesiology) 1984;63:787
Marquez J. High frequency ventilation 1984;63:787
Marquez J. Perspectives in high frequency ventilation 1984;63:378
Marshall M. Neuroanesthesia: current topics in anaesthesia, volume 3 1981;60:126
Martin D. Intensive care of the surgical cardiopulmonary patient 1984;63:379
Martin JT. Positioning in anesthesia and surgery 1979;58:161
Martz KV, Jointer J, Shepherd RM. Management of the patient–ventilator system, a team approach 1980;59:83
Marx GF, Bassell GM. Clinical management of the mother and newborn 1980;59:84
Marx GF, Bassell GM. Obstetric, analgesia and anesthesia, monographs in anaesthesiology 1980;59:957
Matsumoto T. Pre- and postoperative evaluation of surgical procedures 1980;59:228
Mayer BW. Pediatric anesthesia: a guide to its administration 1981;60:698
McKenzie R. Management of labor 1984;63:173
McMinn RMH, Hutchings RT. Color atlas of human anatomy 1983;62:703
Melmon KL, Morrelli HF. Clinical pharmacology 1978;57:600
Miller RD. Anesthesia, volumes 1 and 2 1982;61:165
Modell W. Drugs of choice 1983;62:243
Moir DD. Obstetric anaesthesia and analgesia 1977;56:759
Molitch ME. Management of medical problems in surgical patients 1982;61:1027
Mushin WW, Rendell-Baker L, Thompson PW, Mapleson WW. Automatic ventilation of the lungs, third edition 1980;59:522
Nadel JA. Physiology and pharmacology of the airways 1981;60:171
Norman J, Moles M. Management of the injured patient 1979;58:355
Nunn JF. Applied respiratory physiology, second edition 1980;59:85
Oh TE. Intensive care manual 1981;60:915
Orr RA. Respiratory monitoring in intensive care 1984;63:171
Owens WD. International anesthesiology clinics: anesthetic side effects: seeking, finding, and treating 1981;60:126
Paris P. Trauma 1984;63:95
Parkhouse J, Pleuvry BJ, Rees JMH. Analgesic drugs 1980;59:521
Payne JP, Bushman JA. Artificial ventilation 1981;60:541
Petty TL, Cherniack RM. Seminars in respiratory medicine 1980;59:167
Philbin DM. Anesthetic management of the patient with cardiovascular disease 1979;58:445
Phillips GD, Odgers CL. Parenteral and enteral nutrition 1981;60:70
Popp AJ, Bourke RS, Nelson LR, Kimelberg HK. Neural trauma 1979;58:354
Prior PF. Monitoring cerebral function 1980;59:84
Prys-Roberts C. Hypertension, ischemic heart disease and anesthesia, International Anesthesiology Clinics, winter 1980, volume 18, number 4 1981;60:367
Prys-Roberts C. The circulation of anaesthesia, applied physiology and pharmacology 1980;59:895
Pütsep E. Modern hospital 1980;59:317
Quimby CW Jr. Anesthesiology, a manual of concept and management, second edition 1980;59:85
Quimby CW. Law for the medical practitioner 1980;59:715
Radnay PA. International Anesthesiology Clinics—Anesthetic considerations for pediatric cardiac surgery, volume 18, number 1 1980;59:813
Rarey KP, Youtsey JW. Respiratory patient care 1981;60:916
Rattenborg CC, Via-Reque E. Clinical uses of mechanical ventilation 1982;61:959
Rau JL Jr. Respiratory therapy pharmacology 1979;58:67
Ravin MB. Problems in anesthesia: a case study approach 1982;61:311
Ream AK, Fogdall RP. Acute cardiovascular management—anesthesia and intensive care 1983;62:622
Rehn J. Der alte mensch in der chirurgie 1980;59:227
Reichard SM, Reynolds DG, Adams RR. Advances in shock research, volume X 1983;62:1139
Reichard SM, Wolfe RR. Advances in shock research, volume IX 1983;62:1139
Reyes-Guerra A. Modern anesthesia in dentistry 1980;59:227
Richards JR, Kinney JM. Nutritional aspects of care in the critically ill 1980;59:317
Rinaldo J. Update: pulmonary diseases and disorders 1984;63:171
Roberts RB. Pulmonary aspiration 1977;56:759
Robin ED. Extrapulmonary manifestations of respiratory disease 1979;58:67
Roemer MI. Ambulatory health services in America: past, present and future 1982;61:398
Rollason WN. Electrocardiography for the anaesthetist 1980;59:637
Rosen M, Latto IP, Shang W. Handbook of percutaneous central venous catheterisation 1982;61:398
Roskamm H, Schmuziger M. Coronary heart surgery 1980;59:318
Rothschild JM. Synopsis of critical care 1984;63:787
Safar P (ed). Advances in cardiopulmonary resuscitation 1978;57:290
Saidman LJ, Smith NT. Monitoring in anesthesia 1978;57:601
Sanders JH, Gardner LB. Handbook of medical emergencies 1980;59:228
Scarpelli EM, Auid PAM, Goldman HS. Pulmonary disease of the fetus, newborn and child 1979;58:68
Schieber RA. Fundamentals of tracheal intubation 1984;63:706
Sclabassi SE. Evaluation review (a journal of applied social research) 1984;63:626
Schultz RC. Outpatient surgery 1980;59:318
Shapiro BA. Harrison RA, Trout CA, Clinical application of respiratory care, second edition 1980;59:896
Shapiro BA. Harrison RA, Walton JR: Clinical application of blood gases (2nd ed) 1977;56:881
Shepherd JT, Vanhoutte PM. The human cardiovascular system 1980;59:715
Shibata S, Carrier O. Factors influencing vascular reactivity. 1978;57:600
Shimosato S. Anesthesia and cardiac performance in health and disease 1983;62:1139

**Book reviews**—*continued*
- Shnider SM, Levinson G. Anesthesia for obstetrics 1980;59:522
- Shoemaker WC, Tavares BM (eds). Physiology, monitoring and therapy of the critically ill patient 1978;57:154
- Siegel JH, Chodoff P. The aged and high risk surgical patient: medical, surgical and anesthetic management 1977;56:758
- Simon RR, Brenner BE. Procedures and techniques in emergency medicine 1983;62:863
- Slonim NB, Hamilton LH. Respiratory physiology, fourth edition 1982;61:73
- Smith NT, Miller RD, Corbascio AN. Drug interactions in anesthesia 1981;60:621
- Smith RM. Anesthesia for infants and children, 4th ed 1981;60:70
- Snow JC. Manual of anesthesia 1978;57:291
- Spiro SR. Pain and anxiety control in dentistry 1981;60:847
- Spooner RB. Hospital electrical safety simplified 1980;59:958
- Stanski DR, Watkins WD. Drug disposition in anesthesia 1983;62:622
- Stanton-Hicks Md'A. International anesthesiology clinics: regional anesthesia: advances and selected topics 1979;58:162
- Stark DC. Practical points in anesthesiology 1981;60:233
- Stehling LC. Common problems in pediatric anesthesia 1983;62:543
- Stehling LC, Zauder HI. Anesthetic implications of congenital anomalies in children 1981;60:541
- Steward DJ. Manual of pediatric anesthesia 1980;59:167
- Stool S. Fiberoptic endoscopy in anesthesia 1984;63:471
- Strauch MJ. Pharmacology of respiratory therapy medications 1979;58:533
- Swerdlow M. Relief of intractable pain 1979;58:69
- Sykes MK, Vickers MD, Hull CJ. Principles of clinical measurement 1981;60:847
- Tabatabai M. Calcium regulation by calcium antagonists 1984;63:547
- Tabatabai M. Degradation of endogenous opioids—its relevance in human pathology and therapy 1984;63:547
- Tan LT, Tan MYC, Veith I. Acupuncture therapy: current chinese practice (2nd ed) 1977;56:172
- Tarhan S. Cardiovascular anesthesia and postoperative care 1982;61:958
- Tarrow AB, Erickson JC. Basic and clinical sciences in anesthesiology, ninth edition 1981;60:126
- Tavares BM, Frey R. Acute care 1980;59:319
- The Hastings Center. IRB—review of human subjects research 1981;60:458
- Thibeault DW, Gregory GA. Neonatal pulmonary care 1981;60:848
- Thompson DR. The pharmacologic approach to the critically ill patient 1984;63:706
- Thornton JA. Adverse reactions to anaesthetic drugs 1982;61:550
- Torpey DJ. Cardiac anesthesia, volume 2, cardiovascular pharmacology 1984;63:377
- Tosteson DC, Ovchinnikov YA, Latorre R. Membrane transport processes (vol 2) 1978;57:384
- Trebach AS. The heroin solution 1983;62:959
- Trubuhovich RV. Management of acute intracranial disasters 1979;58:535
- United States Pharmacopeial Convention. 1981 United States pharmacopeia dispensing information 1981;60:699
- Vandam LD. To make the patient ready for anesthesia: medical care of the surgical patient 1981;60:171
- Vander Salm TJ. Atlas of bedside procedures 1980;59:228
- Varkey GP. Anesthetic considerations in the surgical repair of intracranial aneurysms 1982;61:890
- Vickers MD. Medicine for anaesthetists 1983;62:372
- Vickers MD. Wood-Smith FG, Stewart HC. Drugs in anaesthetic practice 1979;58:163
- Volpitto PP, Vandam LD. Genesis of contemporary American anesthesiology 1983;62:703
- Warren FZ. Handbook of medical acupuncture 1977;56:171
- Waterhouse M. Practical mathematics in allied health 1980;59:637
- Watkins J, Ward AM. Adverse response to intravenous drugs 1979;58:162
- Westman HR. MCQ Tutor, anaesthesia, 2nd ed. 1984;63:705
- Westman HR. Medical examination review, vol. 12, anesthesiology, 6th ed. 1984;63:705
- Westman HR. Pain management 1984;63:705
- Westman HR. Recovery room care 1984;63:172
- Widdicombe JG (ed). Respiratory physiology (vol II) 1978;57:384
- Wilkinson PL, Ham J, Miller RD. Clinical anesthesia 1980;59:638
- Wilks DH. Advances in anesthesia, volume 1 1984;63:1145
- Willatts SM. Lecture notes on fluid and electrolyte balance 1983;62:127
- Wilson F, Park WG. Basic resuscitation and primary care 1981;60:458
- Woelfel SK. Techniques of blood transfusion 1984;63:628
- Woo SW. Ambulatory anesthesia care, International Anesthesiology Clinics, volume 20 1982;61:807
- Wood M, Wood AJ. Drugs and anesthesia 1983;62:127
- Woolf CR. The clinical core of respiratory medicine 1982;61:1027
- Wyant GM. Mechanical misadventures in anesthesia 1979;58:262
- Zauder HL. Anesthesia for orthopaedic surgery 1980;59:813
- Ziment I. Respiratory pharmacology and therapeutics 1979;58:447
- Zorab JSM, Baskett PJF. Immediate care 1978;57:517

**Bottle,** see Equipment

**Brachial plexus,** see Anatomy

**Bradycardia,** see Heart, arrhythmia

**Brain**
- anoxia
  - phenytoin in ischemia 1979;58:165
  - reduction of potassium accumulation by phenytoin 1981;60:41
- blood flow
  - cerebral, and nitroprusside (correspondence) 1978;57:142
  - during cardiopulmonary resuscitation 1981;60:73
  - effects of cardiopulmonary bypass (abstract) 1983;62:274
  - halothane and enflurane 1976;55:100
  - isoflurane and halothane anesthesia 1984;63:557
  - isoflurane, effect with or without 50% nitrous oxide 1983;62:499
- carotid endarterectomy 1982;61:631
- computerized axial tomography, of head, and near drowning 1978;57:359
- convulsions
  - fentanyl-induced 1984;63:489
  - following nitrous oxide in mice 1980;59:19
  - halothane and enflurane anesthesia 1976;55:100
  - ketamine suppression of chemically induced convulsions in infant cockerel 1980;59:406
- delirium, following nitrous oxide in mice 1980;59:19
- electroencephalogram
  - enflurane, relationship of abnormalities 1977;56:509
  - postoperative, abnormalities following halothane 1978;57:244
- electroencephalography
  - during cardiopulmonary bypass surgery 1984;63:946
  - during high-dose fentanyl–, sufentanil–, or morphine–oxygen

    - anesthesia 1984;63:386
    - EEG activity and nitrous oxide 1981;60:283
    - effects of fentanyl 1984;63:489
    - neonatal patterns as affected by maternal drugs during labor and delivery 1978;57:303
    - prognostic use in surgery 1983;62:186
    - reduction of enflurane-induced spike activity by scopolamine 1980;59:417
  - endorphin, role in mediating analgesia from transcutaneous electrical stimulation 1981;60:81
  - endorphins
    - CSF clearance (abstract) 1983;62:272
    - effect of general anesthesia and surgical stress on plasma immunoreactivity (abstract) 1983;62:287
  - evoked potentials
    - effects of anesthetics on brainstem auditory evoked responses 1982;61:338
    - lidocaine and dental-evoked potentials 1981;60:779
  - evoked responses
    - changes with retraction of eighth cranial nerve 1981;60:835
    - effects of enflurane 1982;61:898
    - fentanyl–morphine effects 1984;63:833
  - function, anesthetics and murine intelligence 1981;60:794
  - gas embolism, encephalography (case history) 1976;55:141
  - intracranial pressure
    - adenosine triphosphate-induced hypotension 1984;63:381
    - during nifedipine-induced hypotension 1983;62:1078
    - during tetrodotoxin-induced hypotension 1984;63:1005
    - effect of CSF volume 1983;62:581
    - effects of high-frequency jet ventilation 1984;63:1065
    - effects of succinylcholine, *d*-tubocurarine, and dimethyltubocurarine (abstract) 1981;60:269
    - effects of succinylcholine (letter) 1984;63:620
    - failure of enflurane in altering renal responses to 1978;57:200
    - fluctuating hypertension due to Cheyne-Stokes respiration 1977;56:216
    - lidocaine or thiopental 1980;59:435
    - negative end-expiratory pressure and (abstract) 1981;60:238
    - preoperative computed tomography scans 1982;61:430
    - rapid reduction, thiopental versus lidocaine (abstract) 1980;59:528
  - ischemic brain injury
    - effect of heparin 1976;55:683
  - nucleus reticularis, halothane-induced changes 1980;59:897
  - nucleus reticularis gigantocellularis, suppression of neurons 1982;61:763
  - opiate receptors, role in anesthesiology 1980;59:874
  - pH, cerebral surface, changes during asphyxia, hypotension, and circulatory arrest in dog 1977;56:817
  - pituitary
    - alcohol-induced adenolysis and cancer pain 1979;58:279
    - alcohol-induced adenolysis of, control of intractable cancer pain 1977;56:414
    - cholinergic action of thiopental on hypothalamohypophyseal axis 1981;60:310
  - preservation 1981;60:821
  - seizures, neurologic outcome of cardiac arrest (abstract) 1980;59:537
  - serotonin, pain and CNS serotonin 1981;60:854
  - synapses, organization of central synapses 1983;62:1100
  - thiopental protection, neuropsychiatric complications of bypass 1982;61:903
  - vasomotor center, effects on blood pressure 1984;63:482

**Bremazocine,** see Analgesics

**Bretylium,** see
  - Heart,arrhythmias
  - Neuromuscular relaxants

**Bromide,** see Ions

**Bronchofiberscope,** see Equipment

**Bronchopleural fistula,** see Complications

**Bronchospasm,** see
  - Complications
  - Lung

**Bronchus,** see Lung

**Bupivacaine,** see Anesthetics, local

**Buprenorphine,** see Analgesics

**Burns,** see
  - Complications
  - Electrical systems

**Butrophanol,** see Analgesics

**Calcium,** see Ions

**Cancer**
  - chemotherapy and implications for the anesthesiologist 1981;60:425
  - immunosuppression, halothane 1980;59:666
  - serum cholinesterase levels 1979;58:82
  - volatile anesthetics, trace concentrations of 1978;57:328

**Cannulation,** see
  - Anatomy
  - Arteries
  - Specific vessels
  - Veins

**Capacitance respirometry,** see
    - Measurement techniques

**Carbon dioxide**
  - absorption, in infant circuit with water vaporizer 1978;57:307
  - acetazolamide, treatment of metabolic alkalosis 1981;60:608
  - arterial-alveolar gradients, relationship during anesthesia and influencing factors 1981;60:508
  - cardiopulmonary bypass, effect of Pa$_{CO_2}$ on oxygen consumption 1976;55:269
  - cutaneous, evaluation of monitoring (abstract) 1981;60:270
  - embolism
    - death after laparoscopy delayed by "trapping" in portal circulation 1978;57:232
    - during laparoscopy 1977;56:650
  - extracorporeal circulation, low-frequency positive pressure ventilation with 1978;57:470
  - humidified nonrebreathing system (brief reports) 1975;54:271
  - hypercarbia, with acute cardiac tamponade 1983;62:181
  - hypocarbia
    - acute hypnocapneic hypokalemia 1977;56:786
    - effect on myocardial function 1984;63:991
    - effects on electrically stimulated atrial arrhythmias in digitalized dogs 1981;60:302
    - mechanical hyperventilation 1980;59:839
    - with acute cardiac tamponade 1983;62:181
  - laser microsurgery, larynx and trachea (brief reports) 1976;55:146
  - level in circle system 1976;55:706
  - measurement, detecting anesthesia circuit dysfunction 1984;63:536
  - monitoring (abstract) 1984;63:275
  - output
    - anesthetized patient 1975;54:206
    - noninvasive measurement 1980;59:263
  - production, continuous $\dot{V}O_2$ and $\dot{V}CO_2$, measurements during endotracheal anesthesia 1982;61:362
  - tension
    - cutaneous, intraoperative monitoring (abstract) 1982;61:223
    - during anesthesia 1983;62:1065
    - general anesthesia 1982;61:950
    - P$_{CO_2}$ monitoring in neuroanesthesia (abstract) 1981;60:270
    - transcutaneous, relationship in nitrous oxide–fentanyl and nitrous oxide–enflurane anesthesia 1981;60:504
  - thermometric estimation of carbon dioxide output 1975;54:206
  - titration, acid base disorders 1975;54:299

**Carboxyhemoglobin,** see Carbon dioxide

**Cardiac output,** see Heart

**Cardiac output**—*continued*
  profound hypothermia
    infants 1975;54:660
**Cardiovascular anesthesia,** see Anesthesia
**Cardiovascular system,** see
  Arteries
  Heart
  Reflexes
  Veins
**Carlen's tube,** see
  Anesthesia, thoracic
  Anesthetic techniques, endobronchial
  Surgery, thoracic
**Carotid body,** see Receptors, chemoreceptors
**Carotid endarterectomy,** see Surgery, neurologic
**CAT scan,** see Brain, computerized axial tomography
**Catecholamines,** see Sympathetic nervous system
**Catheterization, cardiac,** see Heart
**Catheters,** see Equipment
**Caudal anesthesia,** see Anesthetic techniques, epidural
**Causalgia,** see Pain
**Celiac plexus,** see
  Anatomy
  Anesthetic techniques, regional
  Sympathetic nervous system
**Centbucridine,** see Anesthetics, local
**Cephalothin,** see Antibiotics
**Cephapirin,** see
  Antibiotics
  Brain, blood flow
  Brain, cerebral blood flow
**Cerebrospinal fluid**
  (abstract) 1984;63:180
  $\beta$-endorphin, elimination characteristics 1984;63:511
  density, variability (letter) 1982;61:803
  osmolality, effects on anesthetic requirement, compared with brain sodium and potassium 1978;57:404
  pH, effect on spinal anesthesia 1975;54:455
  pressure
    during oxygen encephalography 1976;55:849
    effect of succinylcholine 1983;62:1006
    fluctuating intracranial, due to Cheyne-Stokes respiration 1977;56:216
    laryngoscopy during intubation 1975;54:687
  production, effects of halothane and fentanyl 1983;62:581
  reabsorption, effects of halothane and fentanyl 1983;62:581
**Cesarean section,** see Anesthesia, obstetric
**Chemodectoma,** see Surgery
**Chemoreceptors,** see Receptors, chemoreceptors
**Chemotherapy,** see Cancer
**Cheyne-Stokes,** see Ventilation
**Children,** see Anesthesia, pediatric
**Chloralose** see Pharmacology
**Chloramphenicol,** see Antibiotics
**Chloroform,** see Anesthetics, volatile
**Chloroprocaine,** see Anesthetics, local
**Choledochoduodenal sphincter,** see Anesthesia, biliary tract surgery
**Cholinesterase,** see Enzymes
**Chronotropy,** see
  Heart, atria
  Heart, pulse rate
  Heart, sinoatrial node
**Chymopapain,** see Allergy
**Cilia,** see
  Lung, tracheal cilia
  Lung, bronchi
**Cimetidine,** see
  Gastrointestinal tract, gastric pH
  Gastrointestinal tract, stomach
  Histamine
  Pharmacology
**Circuits, anesthetic,** see
  Anesthetic techniques
  Equipment, circuits
**Cirrhosis,** see Liver
**Citrate,** see
  Antacids
  Gastrointestinal tract, antacids
**Clindamycin,** see Antibiotics
**Clonidine,** see Sympathetic nervous system, alpha-adrenergic agonists
**Closed circuits,** see Equipment, circuits
**Cluneal nerve,** see
  Complications, neuropathy
  Nerve, cluneal
**Coagulation,** see Blood
**Cocaine,** see Anesthetics, local
**Codeine,** see Analgesics, narcotic
**Coma,** see Complications
**Compliance,** see
  Heart
  Lung
**Complications**
  acupuncture in obstetrics 1975;54:83
  acute ethanol intoxication (brief reports) 1976;55:602
  acute hypotension during laparoscopy 1975;54:142
  acute maxillary sinusitis, nasotracheal intubation (brief reports) 1976;55:885
  acute renal failure, pancuronium 1976;55:343
  acute respiratory failure 1976;55:195
  adult respiratory distress syndrome, pancuronium 1975;54:219
  airway obstruction
    mediastinal Hodgkin's disease (case history) 1975;54:399
  alopecia 1980;59:311
    (letter) 1984;63:1142
    telogen effluvium 1984;63:83
  anaphylaxis management 1976;55:493
  anesthesia death
    liability (physician and the law) 1976;55:759
    no negligence in surgeon's failure to supervise (physician and the law) 1976;55:459
  angioneurotic edema, anesthetic and perioperative management of patient with 1977;56:571
  arterial hypoxemia, caused by intravenous ketamine 1976;55:311
  arthritis, anesthetic management in 1981;60:611
  arthritis, rheumatoid, cricoarytenoid joints 1975;54:742
  aspiration
    antacids and gastric acid neutralization 1984;63:325
    antacids in rabbits 1982;61:288
    blind esophageal intubation to divert gastric contents (correspondence) 1977;56:598
    effects of intravenous cimetidine and metoclopramide 1984;63:599, 1014
    laryngospasm as early indicator of 1978;57:119
    (letter) 1984;63:1142
    pneumonia prophylaxis (editorial) 1983;62:1055
    preanesthetic glycopyrrolate and cimetidine 1984;63:40
    pulmonary effects of volume and pH 1984;63:665
    silent gastropharyngeal regurgitation during anesthesia 1981;60:655
    tracheal 1976;55:816
  aspirin intolerance 1975;54:376
  asthma
    bronchial pharmacology (editor's choice) 1975;54:227
    perioperative management 1984;63:844
  atelectasis, during anesthesia 1980;59:792
  atypical pseudocholinesterase 1976;55:243
  auditing, incidence 1984;63:611
  Bartter's syndrome, anesthetic implications 1981;60:764
  blindness, following attempted stellate ganglion block 1981;60:689
  bradycardia and junctional rhythm, following succinylcholine, atropine 1975;54:705
  brain damage
    cardiac arrest (physician and the law) 1975;54:778
    during appendectomy (physician and the law) 1976;55:45
  bronchopleural fistula, use of intraoperative dual-mode independent lung 1981;60:118
  bronchopleural-cutaneous fistula (brief reports) 1976;55:874

bronchospasm 1983;62:104
bronchospasm during anesthesia 1975;54:783
bupivacaine, compared with etidocaine for vaginal delivery 1975;54:250
burns
  diazepam kinetics 1983;62:293
  (letter) 1984;63:1141
  pharmacokinetics of *d*-tubocurarine 1982;61:241
  transcutaneous electronerve analgesia (letter) 1982;61:801
cardiac arrest
  after intratracheal epinephrine 1984;63:829
  asystole after single dose of succinylcholine 1978;57:135
  cardiopulmonary resuscitation with interposed abdominal compression 1982;61:645
  following pneumonectomy and pericardiotomy 1978;57:501
  with electromechanical dissociation 1978;54:498
cardiac catheterization, hydromediastinum after 1980;59:159
cardiac decompensation, during enflurane anesthesia (case history) 1976;55:433
cardiac failure, associated with hypocalcemia 1976;55:34
cardiovascular collapse, following phytonadione (brief reports) 1976;55:304
cardiovascular effects, of isoflurane and halothane during controlled ventilation 1975;54:701
catheter tip design, influence on tracheobronchial trauma and fluid aspirations efficiency 1976;55:290
choledochoduodenal sphincter spasm, biliary spasm and fentanyl 1981;60:638
circulatory changes, during anesthetic induction 1976;55:77
coma, hyperglycemic, following diazoxide 1977;56:506
congenital lobar emphysema (case history) 1976;55:869
corneal injuries, during general anesthesia 1975;54:465
cricothyroid membrane puncture (case history) 1976;55:299
decreased arterial oxygenation, sodium nitroprusside (brief reports) 1976;55:880
defective disposable endotracheal tube (brief reports) 1976;55:437
dental, traumatic tooth avulsion 1982;61:469
Dercum's disease, management of intractable pain with intravenous lidocaine 1976;55:257
difficult extubation of an endotracheal tube cuff (brief reports) 1976;55:876
diffuse bleeding, diathesis of uncertain origin 1976;55:173
disconnections (letter) 1983;62:1134
Down's syndrome, congenital lobar emphysema (case history) 1976;55:869
drug interaction, muscle relaxants and antibiotics 1976;55:224
drug-drug interactions (editor's choice) 1975;54:76
dystonia musculorum deformans 1984;63:616
Ebstein's anomaly, prolonged induction in 1981;60:909
edema, progesterone for Pickwickian syndrome, respiratory implications 1977;56:133
effect of halothane on isometric twitch and tetanus response 1975;54:527
effect of heparin on recovery from ischemic brain injuries 1976;55:683
effect of ketamine on cardiovascular dynamics 1975;54:588
effect of morphine on renal function 1975;54:357
effect of patient age, pH of cerebrospinal fluid and vasopressors on spinal anesthesia 1975;54:455
Eisenmenger syndrome, general anesthesia in presence of 1977;56:543
electroconvulsive therapy in a parturient 1975;54:203
electrocorticographic seizure activity 1975;54:722
embolism, air 1975;54:792
emergency surgery during acute myocardial infarction (case history) 1975;54:267
endotracheal intubation
  croup in children 1977;56:501
  sublingual hematoma following laryngoscopy 1979;58:343
  vocal cord paresis following (questions and answers) 1977;56:321
epidermolysis bullosa
  emergency cesarean section with 1978;57:281
  ketamine anesthesia in 1977;56:398
epidural abscess, following spinal anesthesia 1978;57:351
epidural blood patch 1975;54:459
epiglottitis
  children 1975;54:622
  criteria for extubation (abstract) 1982;61:211
  duration of intubation and fever 1983;62:785
  extubation criteria for children (letter) 1984;63:468
esophageal stethoscope, tracheal insertion of 1977;56:584
ether skin prep, use of electrocautery (questions and answers) 1975;54:210
exposure 1975;54:449
fatality from swallowed denture, following prolonged endotracheal intubation (brief reports) 1976;55:438
fibrinogen and albumin deficiencies, associated with packed red blood cell transfusions 1975;54:89
fire hazard, ASA committee, operating room humidity (questions and answers) 1976;55:134
fire hazard, carbon dioxide laser microsurgery (brief reports) 1976;55:146
fires, nonflammable in operating room (case history) 1975;54:152
fires, potential ignition source in operating room 1976;55:217
fluroxene toxicity 1976;55:529
gas embolism, encephalography (case history) 1976;55:141
general anesthesia, mental aberrations 1975;54:609
Hallermann-Streiff syndrome, anesthetic management 1979;58:254
hazards
  in use of anode endotracheal tube 1975;54:710
  of disposable rebreathing circuits (brief reports) 1976;55:743
headache
  postdural puncture, chronic pain 1980;59:772
  spinal, epidural anesthesia following epidural blood patch 1978;57:272
heart block and artificial cardiac pacemakers, anesthesia for patients with 1976;55:626
heart failure after cardiopulmonary bypass, vasodilation (case history) 1975;54:842
hematoma, epidural blood patch technique 1980;59:702
hiccups, technique to stop during endotracheal intubation (letter) 1981;60:121
homocystinuria, anesthetic considerations and 1982;61:708
humidification, indications and hazards in respiratory therapy 1975;54:444
hypercapnia, during cyclopropane anesthesia (brief reports) 1976;55:439
hypertension, Wilms' tumor 1976;55:519
hypertension and decreased renal blood flow, following methylene blue injection 1976;55:674
hypotension, comatose hemophiliac child 1976;55:346
hypothermia, during cystoscopy in neonates (brief reports) 1976;55:592
inadequate epidural analgesia 1975;54:593
inadvertent epidural injection of thiopental (brief reports) 1975;54:406
increased cerebrospinal fluid pressure 1975;54:687

**Complications**—*continued*
- increased succinylcholine, following *d*-tubocurarine pretreatment 1975;54:282
- infarction, anesthesia for patients early after 1976;55:640
- infections
    - effect of succinylcholine on serum potassium 1983;62:327
    - with gas gangrene 1976;55:247
- innominate artery compression, simulating cardiac arrest during mediastinoscopy 1976;55:748
- interaction of epinephrine with enflurane, isoflurane and halothane 1976;55:709
- interscalene cervical plexus block 1975;54:370
- intramuscular ketamine, pediatric radiotherapy 1976;55:92
- intraocular pressure
    - electroshock therapy 1975;54:479
    - following enflurane anesthesia 1975;54:212
- intubation, endotracheal, management, prone position 1980;59:700
- ketamine, in pediatric dentistry 1975;54:248
- kyphoscoliosis, epidural anesthesia for cesarean section in 1978;57:125
- laryngeal stenosis in acromegaly 1976;55:57
- laryngotracheal residue during endotracheal anesthesia 1976;55:392
- lincomycin-curare interaction 1975;54:103
- lorazepam reveral 1975;54:607
- lumbar epidural anesthesia, effect on fetal heart rate 1975;54:779
- lumbar puncture, CSF cutaneous fistula (case history) 1975;54:691
- lumbosacral plexus block 1976;55:350
- malignant hyperpyrexia, preplanned treatment 1976;55:713
- malignant hyperthermia, enflurane 1975;54:47
- medullary narcosis (editor's choice) 1975;54:579
- meningitis, spinal anesthesia 1983;62:513
- meningoencephalocele, anesthesia induction in infant with, and frontal dysplasia 1977;56:736
- methoxyflurane biotransformation, and renal function 1976;55:415
- multiple exposures, halothane 1975;54:332
- muscular dystrophy, anesthetic hazard 1975;54:212
- muscular dystrophy, massive myoglobinuria, halothane and succinylcholine 1976;55:680
- myasthenia gravis
    - and pregnancy 1978;57:441
    - anesthesia for transcervical thymectomy in 1976;55:13
    - atracurium-induced anesthesia 1984;63:1127
    - curare sensitivity in (correspondence) 1978;57:515
    - curare sensitivity in steroid-treated 1978;57:132
    - ester type local anesthetic (questions and answers) 1975;54:506
- myocardial infarction, effects on perioperative cardiac complications 1983;62:493
- myoglobinuria, precipitated by halothane and succinylcholine 1976;55:680
- myotonia atrophia, cardiac decompensation, enflurane (case history) 1976;55:433
- myotonia dystrophica, anesthetic hazard 1975;54:212
- nasotracheal extubation, unusual problem in (brief reports) 1976;55:302
- neurofibromatosis, renal hypertension (case history) 1975;54:542
- neurologic
    - cervical plexus damage, back roll 1982;61:471
    - cluneal, and pain following intragluteal injection 1978;57:138
    - following epidural or spinal anesthesia 1981;60:150
    - intraoperative awakening for early recognition of possible neurologic sequelea during Harrington rod spinal fusion 1976;55:526
    - penicillin (letter) 1979;58:63
    - transient lower extremity weakness 1981;60:527
    - ulnar nerve palsy 1981;60:687
- neuropsychiatric, cardiopulmonary bypass 1982;61:903
- obesity
    - arterial oxygenation 1981;60:691
    - cephalad spread of analgesia following bupivacaine and 1980;59:89
    - comparison of intramuscular and epidural morphine for postoperative analgesia 1984;63:583
    - continuous epidural anesthesia for cesarean section 1979;58:348
    - effect of position on postoperative oxygenation 1976;55:37
    - enflurane blood-gas solubility 1982;61:1006
    - fluoride levels during and after enflurane 1979;58:409
    - gastric secretions 1981;60:37
    - halothane metabolite binding 1981;60:548
    - intubation with modified laryngoscope (letter) 1981;60:120
    - midline incision, postoperative alveolar-arterial oxygen tension difference 1975;54:433
    - postoperative hypoxemia (abstract) 1980;59:534
    - postoperative ventilatory failure 1975;54:523
    - progesterone for Pickwickian syndrome, respiratory implications 1977;56:133
    - prone positioning in (letter) 1981;60:537
    - spread of epidural anesthesia 1981;60:421
    - supine death syndrome 1979;58:345
    - supine death syndrome (letter) 1980;59:81
    - thoracic epidural vs balanced anesthesia 1980;59:902
- occlusion, arterial cannulation 1975;54:836
- paralysis
    - flaccid, following obstetrical epidural anesthesia: possible role of benzyl alcohol 1977;56:219
    - nitroprusside and epidural analgesia 1981;60:61
    - resistance to neuromuscular relaxants, patients with hemiplegia 1980;59:624
- Parkinsonism, levodopa effects on halothane anesthesia 1975;54:178
- parturient with cardiac valve prosthesis 1976;55:214
- pericardectomy, uremic pericardial effusion 1976;55:378
- perioperative awareness and recall 1976;55:513
- phagocytosis during general anesthesia 1975;54:501
- pneumatocele of the larynx (brief reports) 1976;55:600
- pneumocephalus, nitrous oxide 1981;60:57
- pneumonia, effects of positive end-expiratory pressure 1979;58:208
- pneumonitis, preanesthetic glycopyrrolate and cimetidine 1984;63:40
- pneumoperitoneum
    - craniofacial reconstruction 1982;61:146
    - tension (letter) 1982;61:624
- pneumothorax, mechanical ventilation 1975;54:730
- postoperative, in surgery for congenital heart disease 1984;63:657
- postoperative hypoxemia 1976;55:822
- postoperative ventilatory failure, myopathic process 1975;54:523
- postpartum, hypertension and convulsion after oxytocic drugs 1976;55:813
- postspinal headache
    - epidural autologous blood patch treatment on an outpatient basis

(letter) 1984;63:962
  epidural blood patch treatment 1984;63:1033, 1121
priapism
  a therapeutic challenge (letter) 1983;62:1136
  ketamine and physostigmine 1982;61:705
profound hypothermia, infants 1975;54:660
progeria 1979;58:424
prolonged apnea, after succinylcholine (case history) 1976;55:737
prolonged neuromuscular blockade 1976;55:353
propranolol
  and surgical anesthesia 1976;55:01
  in cardiac surgery 1975;54:571
pseudoxanthoma elasticum, anesthetic considerations in 1981;60:344
pulmonary edema 1984;63:363
pulmonary hemorrhage, complicating pulmonary embolectomy 1976;55:182
pulseless disease, anesthetic management 1983;62:532
radiation, and succinylcholine hyperkalemia 1982;61:83
refusal of surgery, following Innovar 1975;54:224
renal effects, metabolism of sevoflurane and methoxyflurane 1975;54:829
renal failure, succinylcholine effect on potassium 1975;54:746
respiratory, and COPD during anesthesia 1983;62:975
respiratory depression, doxapram 1975;54:352
respiratory distress, with cardiovascular anomaly 1976;55:481
respiratory infections, subacute, in small children 1979;58:331
resuscitation
  after intratracheal epinephrine 1984;63:829
  interposed abdominal compression 1982;61:645
reversal of datura stramonium delirium, with physostigmine (brief reports) 1975;54:158
rheumatoid arthritis, cricoarytenoid joints 1975;54:742
Romano-Ward syndrome, stellate ganglion block and idiopathic prolongation of the Q-T interval with cardiac arrhythmia 1976;55:782
Rubinstein-Taybi syndrome, anesthetic problems in 1981;60:534
shearing hazard of intra-arterial Teflon catheters (brief reports) 1976;55:597
sickle cell disease, anesthesia 1975;54:361
spinal cord injuries, anesthesia and autonomic hyperreflexia 1982;61:344
stellate ganglion block 1975;54:567
  subarachnoid intracranial pressure 1975;54:494
  subdissociative dosage, ketamine 1975;54:312
  succinylcholine, avoidance of side effects (questions and answers) 1975;54:637
  supine hypotensive syndrome, intra-abdominal mass (brief reports) 1976;55:887
  thromboembolism, after total hip replacement 1983;62:174
  trachea, epithelium 1975;54:340
  trachea, stenosis 1976;55:191
  tracheal aspiration 1976;55:816
  tracheal bronchus, unusual airway problem (brief reports) 1976;55:746
  tracheal intubation 1984;63:335
  treating acute heroin and methadone toxicity (editor's choice) 1976;55:607
  urticaria, pigmentosa, general anesthesia in a child 1980;59:704
  vanishing lung syndrome, anesthesia 1976;55:750
  ventricular arrhythmias, following epinephrine injection 1975;54:468
  vitrectomy 1975;54:58
  Wegener's granulomatosis, case report and literature review 1978;57:353
  wheezing, negative expiratory pressure 1979;58:49
**Computerized axial tomography,** see Brain
**Computers**
  anesthesia interviews, summary of patients' preanesthesia visit 1980;59:03
  computer assisted instruction, cardiopulmonary resuscitation 1975;54:308
**Conduction,** see Heart
**Conduction anesthesia,** see Anesthetic techniques, epidural, regional, spinal
**Connectors,** see Equipment
**Contrast media,** see Surgery, cardiovascular
**Convulsions,** see
  Anticonvulsants
  Brain
  Complications
  Toxicity
**Coronary,** see Heart, blood flow
**Coronary heart disease,** see Heart
**Corrections**
  first paragraph under discussion in comparison of methotrimeprazine and meperidine as components of balanced anesthesia which appeared 1976;55:46
**Corticosteroids,** see
  Hormones
  Metabolism
**Cosmetic surgery,** see Surgery, plastic
**CPAP,** see Ventilation, continuous positive pressure
**Croup,** see Larynx, edema
**Cryptenamine,** see
  Anesthetic techniques, hypotensive
  Sympathetic nervous system, sympatholytic agents
**Cuffs, endotracheal,** see Equipment
**Curare,** see Neuromuscular relaxants, *d*-tubocurarine
**Cyanide,** see Anesthetic techniques, hypotension-induced, hypotensive, nitroprusside
  Toxicity, nitroprusside
**Cyclopropane,** see Anesthetics, gases
**Dantrolene,** see
  Hyperthermia, malignant
  Neuromuscular relaxants
**Datura stramonium delirium**
  physostigmine (brief reports) 1975;54:158
**Dead space,** see Ventilation
**Defibrillation,** see
  Equipment
  Heart
**Denitrogenation,** see Induction, anesthesia
**Dental anesthesia,** see Anesthesia, dental
**Depth, anesthetic,** see
  Anesthesia
  Individual anesthetics
  Measurement techniques
  Potency, anesthetic
**Dextran,** see
  Anesthetics, local
  Blood replacement
**Dezocine,** see
  Analgesics, narcotic
**Diabetes,** see
  Complications
  Metabolism
**Diacetylmorphine,** see Heroin
**Diamorphine,** see Heroin
**Diazepam,** see
  Anticonvulsants
  Hypnotics, benzodiazepines
  Premedication
**Diazoxide,** see Blood pressure
**Dibucaine,** see Anesthetics, local
**Diethyl ether,** see Anesthetics, volatile
**Diethylstilbestrol,** see Pharmacology
**Digitalis,** see Heart
**Digoxin,** see Heart
**Dimethyltubocurarine,** see Neuromuscular relaxants, metocurine
**Dioxychlorane,** see Anesthetics, volatile
**Diuretics,** see Kidney
**Dobutamine,** see
  Heart
  Sympathetic nervous system
**Domperidone,** see Vomiting, antiemetics
**Dopamine,** see
  Heart

**Dopamine**—*continued*
  Pharmacology
  Sympathetic nervous system, dopamine
**Doppler ultrasound,** see
  Equipment
  Measurement techniques
**Doxepin,** see Ataractics, antidepressants
**Droperidol,** see Anesthetics, intravenous
**Drug addiction,** see Analgesics
**Drug interaction,** see Interactions, (drug)
***d*-tubocurarine,** see Neuromuscular relaxants
**Duration,** see Anesthesia
**Dystonia musculorum deformans,** see Complications
**Dystrophy,** see Sympathetic nervous system
**Ear,** tympanic membrane, rupture with nitrous oxide 1978;57:283
**Ebstein's anomaly,** see Complications
**ECG,** see Heart, electrocardiography
**Echocardiography,** see
  Heart
  Measurement techniques
**Eclampsia,** see
  Anesthesia, obstetric
  Complications
**Edema,** see
  Complications, lung
  Lung
**Edrophonium,** see Antagonists, neuromuscular relaxants
**Education**
  evaluation 1975;54:553
  gossip and acquisition of knowledge 1978;57:519
  lecture slides, visual communication 1976;55:6
  medical students
    anesthesia orientation 1975;54:328
    changing specialties 1982;61:504
    national survey of attitudes of 1979;58:201
    views of anesthesiology (letter) 1979;58:443
  performance evaluation
    continuous lumbar epidural anesthesia 1981;60:543
    correlation between skill and knowledge 1984;63:603
  responsibilities and leadership in health sciences 1981;60:658
**Eisenmenger syndrome,** see
  Complications
  Heart
**Ejaculation,** see Complications
**EKG,** see Heart, electrocardiography
**Electrical systems**
  burns, battery-operated Doppler monitor 1979;58:339
**Electroanesthesia,** see Anesthetic techniques, electronarcosis
**Electrocardiography,** see
  Heart
  Monitoring
**Electroconvulsive therapy,** see Anesthesia, electroshock
**Electrodes,** see
  Complications, burns
  Heart, electrocardiography
  Measurement techniques, oxygen, carbon dioxide, pH
**Electroencephalogram,** see
  Brain
  Monitoring
**Electrolytes,** see
  Ions,
  Acid-Base equilibrium
**Electromyogram,** see
  Measurement techniques
  Muscle, skeletal
**Electroshock therapy,** see Anesthesia
**Embolism**
  air
    (abstract) 1984;63:220, 221
    associated with pulmonary arterial catheters 1984;63:871
    comparison of external cardiac massage, intracardiac aspiration, and left lateral decubitus position 1978;57:166
    direct scintigraphic visualization (abstract) 1983;62:250
    effect of PEEP during sitting neurosurgical procedures (abstract) 1981;60:262
    experimental evaluation of methods used for prevention (abstract) 1983;62:287
    kinetics of (abstracts) 1983;62:250
    nitrous oxide and (letter) 1982;61:956
    postoperative 1980;59:297
    residual intravascular pulmonary gas following 1982;61:304
    venous 1982;61:65
  amniotic fluid, during curettage for missed abortion 1977;56:739
  carbon dioxide, death after laparoscopy delayed by "trapping" in portal circulation 1978;57:232
  gas
    aspiration or carbon dioxide (letter) 1983;62:368
    during laparoscopy 1977;56:650
    encephalography (case history) 1976;55:141
    lasers for urethral surgery (letter) 1982;61:160
  paradoxical, effects of positive end-expiratory pressure 1984;63:429
  therapeutic, chloroprocaine for pain control 1981;60:02
  thromboembolism (letter) 1984;63:374
  venous air, surface-active agent 1975;54:792
**Emergence,** see Recovery
**Endobronchial,** see
  Anesthesia, thoracic
  Anesthetic techniques
  Equipment, endobronchial
  Surgery, thoracic
**Endobronchial techniques,** see Anesthetic techniques
**Endorphins,** see
  Brain
  Polypeptides
**Endotracheal tubes,** see
  Equipment, tubes
  Intubation
**Enflurane,** see Anesthetics, volatile, enflurane
**Enzymes**
  adenylate cyclase
    and phosphodiesterase, halothane effects 1980;59:856
    halothane-induced depression of myocardial contractility 1984;63:285
  cholinesterase
    activity during prolonged succinylcholine infusion 1982;61:941
    activity in bank blood 1980;59:211
    and increased sensitivity to succinylcholine 1978;57:422
    antagonism of phase II block (letter) 1981;60:911
    correlation of plasma activity and duration of succinylcholine during pregnancy 1977;56:78
    inhibitor poisoning in obstetrics (letter) 1983;62:1135
    inhibitor poisoning in pregnant women 1983;62:233
    levels in cancer patients 1979;58:82
    levels, pregnancy 1982;61:953
    measurement of pseudocholinesterase (letter) 1983;62:617
    plasma pseudocholinesterase deficiency, and diethylstilbestrol therapy 1978;57:726
    pseudocholinesterase levels in pregnancy (letter) 1983;62:783
  fructose-1, 6-diphosphatase, anesthetic management of patient with hereditary deficiency 1978;57:503
  methionine synthetase, inactivated by nitrous oxide 1982;61:75
  phosphorylase, susceptibility to malignant hyperthermia 1983;62:324
  pseudocholinesterase
    pseudocholinesterase atypical 1976;55:243
    cocaine and succinylcholine sensitivity 1979;58:235
    succinylcholine-induced fasciculation as indicator of atypical 1984;63:869
**Ephedrine,** see Sympathetic nervous system, sympathomimetic agents
**Epidermolysis bulbosa,** see Complications
**Epidural,** see Anesthetic techniques, epidural
**Epiglottitis,** see Complications

- **Epinephrine,** see
  - Catecholamines
  - Heart, arrhythmias
  - Sympathetic nervous system, epinephrine
- **Equipment**
  - absorbers, soda lime contamination (letter) 1980;59:711
  - advantages of infant ventilators over adapted adult ventilators 1976;55:769
  - airway
    - intubation (letter) 1982;61:309
    - method for blind oral intubation of trachea or esophagus 1977;56:866
  - airways, oral, modification of as bite block (letter) 1980;59:225
  - ampules, sterilization by ethylene oxide (questions and answers) 1977;56:743
  - anesthesia machines
    - detection of faults 1984;63:79
    - disconnections (letter) 1984;63:702
    - gas circuit failure (letter) 1984;63:1047
    - hazards 1976;55:26
    - malfunction (abstract) 1983;62:265
    - malfunction occurring after routine preventive maintenance inspection (letter) 1983;62:701
    - narrow bore tubing (letter) 1984;63:92
    - test for leaks (letter) 1983;62:855
    - unusual disconnection 1983;62:696
  - blood warmer (brief reports) 1975;54:155
  - bottle adapter, for vaporizers, hazards of (correspondence) 1978;57:596
  - breathing bags, resuscitation, manually operated self-inflating 1977;56:202
  - bronchofiberscope, jet ventilation 1980;59:350
  - bronchoscope, fiberoptic
    - for difficult nasogastric intubation 1981;60:904
    - new techniques (letter) 1981;60:617
  - calibration of the Narkotest gas monitor, for isoflurane (brief reports) 1976;55:441
  - Carlens tube 1976;55:340
  - Carlen tube insertions (brief reports) 1976;55:882
  - catheters
    - (abstract) 1984;63:200
    - aspiration efficiency, influence of suction catheter tip design 1976;55:290
    - balloon-tipped, use in bronchial blockade (brief reports) 1976;55:874
    - central venous 1984;63:949
    - central venous pressure 1984;63:953
    - epidural, fusion between catheter and stylet 1980;59:516
    - flow-directed 1983;62:285
    - flow-directed, aortocoronary bypass surgery (abstract) 1982;61:221
    - flow-directed, complications during open heart surgery (abstract) 1983;62:236
    - flow-directed, guide-wire technique replacement 1980;59:455
    - flow-directed, hemoptysis and 1979;58:153
    - flow-directed, indications for (letter) 1982;61:477
    - flow-directed, inflating characteristics 1983;62:363
    - flow-directed, inflation and pressure (letter) 1984;63:467
    - flow-directed, mixed venous blood samples in severely traumatized patients 1977;56:527
    - flow-directed, nitrous oxide and (letter) 1982;61:308
    - intraarterial Teflon, shearing hazard (brief reports) 1976;55:597
    - intracardiac knotting of 1980;59:217
    - intravenous and side port functional gauge 1981;60:06
    - intravenous, displacement of right atrial and endotracheal, with neck flexion 1978;57:371
    - intravenous, for rapid fluid infusion (letter) 1981;60:696
    - introducer for percutaneous cardiovascular catheters (brief reports) 1976;55:148
    - (letter) 1984;63:168, 963
    - pulmonary arterial 1984;63:772, 871
    - pulmonary artery, pathophysiology of rupture by balloon-tipped catheters 1983;62:925
    - Swan-Ganz (brief reports) 1975;54:649
    - Swan-Ganz introducer wire (letter) 1981;60:67
    - technique to replace central venous catheter with pulmonary arterial catheter (letter) 1981;60:229
    - tracheobronchial suction 1976;55:290
    - vascular 1982;61:871
    - venous, comparison of two different J-wires for cannulation via the external jugular vein 1983;62:365
    - venous (letter) 1984;63:1143
  - central venous pressure, Swan Ganz pressure monitor (brief reports) 1975;54:549
  - circuits
    - (abstract) 1984;63:273
    - anesthetic, and inflow requirements (correspondence) 1978;57:750
    - Bain circuit
      - continuous $\dot{V}O_2$ and $\dot{V}CO_2$ measurements during endotracheal anesthesia 1982;61:362
      - characteristics of Bain circuit 1977;56:822
      - evaluation of Bain circuit 1977;56:84
      - fresh gas flow requirement with the Bain circuit during controlled ventilation (abstract) 1983;62:291
      - nonrebreathing, Bain, characteristics of 1977;56:822
    - circle system, relation of $Pa{CO_2}$ to fresh gas flow 1976:55:706
    - circle systems 1976;55:724
    - closed circuits
      - accumulation of methane, acetone, and nitrogen (abstract) 1981;60:267
    - Columbia pediatric circle (brief reports) 1976;55:877
    - compromise for closed system 1978;57:18
    - nonrebreathing
      - characteristics of Bain anesthesia circuit (correspondence) 1978;57:375, 377
      - rebreathing circuits, disposable, (brief reports) 1976;55:743
      - tube support strap (letter) 1982;61:160
    - safety valve for the pediatric Rees system (brief reports) 1976;55:741
  - computed tomography, and intracranial pressure 1982;61:430
  - connectors, faulty Y-piece (letter) 1981;60:121
  - "continuously-on" suction valve (brief reports) 1975;54:695
  - cuffs, endotracheal tubes
    - changes in and, intrathoracic large airway circumference 1982;61:693
    - clinical evaluation 1980;59:291
    - herniation of, as cause of airway obstruction 1978;57:114
    - high volume, low pressure airway cuffs 1975;54:340
    - low pressure endotracheal tube cuffs (brief reports) 1976;55:595
    - pathology following short-term intubation with 1978;57:577
    - significance of $P{CO_2}$ (brief reports) 1976;55:595
  - disconnections (letter) 1983;62:1134
  - Doppler ultrasound
    - blood pressure monitoring 1979;58:526
    - electrosurgical burn and 1979;58:339
  - ECG lead, precordial (brief reports) 1976;55:740
  - ECG monitor, rechargeable (questions and answers) 1976;55:613
  - exhaust systems
    - hazards of an anesthetic scavenging device (letter) 1983;62:458
    - ventilator alarm nonfunction 1983;62:230
    - cost of scavenging (editorial) 1979;58:265
    - Dräger scavenging interface system for wall suction 1979;58:327
    - gas evacuator, Jackson-Rees system (brief reports) 1976;55:881
    - gas scavenging (brief reports) 1976;55:881

**Equipment**—*continued*
- exhaust system—*continued*
  - gas scavenging (letter) 1982;61:162
  - hazards of gas scavenging 1978;57:286
  - hazards of scavenging systems (letter) 1980;59:162
  - mechanical aspects of anesthetic pollution control 1977;56:769
  - monitoring occupational exposure to inhalation anesthetics 1977;56:778
  - operating room pollution, governmental perspectives and guidelines 1977;56:775
  - pediatric, waste gas scavenging valve for 1977;56:291
  - pneumothorax from suction applied to ventilator 1979;58:147
  - scavenging of anesthetic gases (letter) 1980;59:163
  - servo systems, comparison of anesthetist and machine performance 1984;63:715
  - servo systems, control of arterial blood pressure during halothane anesthesia 1982;61:1010
- filters
  - bacterial, resistance in (correspondence) 1978;57:515
  - blood filters for massive transfusions (questions and answers) 1975;54:45
  - blood filters in respiratory failure (abstract) 1980;59:539
  - gas line, cause of hypoxia 1980;59:617
  - pore size of filters (questions and answers) 1975;54:45
  - respiratory-circuit bacterial, water-induced resistance in 1978;57:269
  - transfusion 1978;54:463
- head straps 1980;59:457, (letter) 1980;59:808
- heart assist, left, postperfusion low cardiac output 1977;56:402
- humidifiers
  - adult body temperature and heated humidification of anesthetic gases during general anesthesia 1981;60:736
  - alteration of halothane (letter) 1980;59:518
  - anesthetic gases 1979;58:216
  - artificial noses for use during endotracheal anesthesia 1983;62:758
  - body temperature decrease (letter) 1982;61:393
  - contamination, by bacteria 1978;57:191
  - heated water humidifier with rotating wick 1979;58:244
  - immersion heater humidifiers 1976;55:331
  - infant circuit, warmed by carbon dioxide neutralization 1978;57:307
  - (letter) 1983;62:460
  - maintenance of body temperature 1976;55:719
  - nonrebreathing system (brief reports) 1975;54:271
  - of anesthetic systems 1975;54:50
  - Pall bacterial filter 1984;63:566
  - percolator vaporizer 1981;60:146
- laryngoscope
  - bulb (questions and answers) 1975;54:505
  - fiberoptic 1977;56:126
  - fiberoptic, guide and protector 1977;56:126
  - fiberoptic stylet 1984;63:161
  - fiberoptic with remote light source 1981;60:841
  - indirect-direct laryngoscope (brief reports) 1975;54:404
  - modified for intubation of obese patients (letter) 1981;60:120
  - pediatric use (letter) 1983;62:241
- lasers
  - anesthesia for surgery 1983;62:218
  - fire hazards (letter) 1982;61:546
  - microsurgery, larynx and trachea (brief reports) 1976;55:146
  - urethral surgery (letter) 1982;61:160
- microwave
  - physiologic effects of rewarming, possible application for neonatal cardiac surgery 1979;58:297
  - rewarming (letter) 1980;59:161
- monitoring, hemodynamic tracking system 1980;59:169
- nebulizers
  - aerosol anesthesia of airway 1980;59:803
  - contamination (correspondence) 1978;57:748, 749
  - for anesthesia circuits (letter) 1981;60:537
- needles
  - comparison of insulated and uninsulated needles for locating peripheral nerves 1984;63:925
  - comparison of insulated vs uninsulated needles for electrical nerve location 1984;63:919
  - Lee modification of the Tuohy needle (letter) 1984;63:1048
  - Tuohy in paramedian approach for peridural block 1977;56:582
- nerve stimulators
  - comparison of insulated and uninsulated needles for locating peripheral nerves 1984;63:925
  - comparison of insulated vs uninsulated needles for electrical nerve location 1984;63:919
  - competitive neuromuscular block 1975;54:649
  - for monitoring and performing neuromuscular blockade 1978;57:13
  - peripheral nerve stimulator (questions and answers) 1975;54:297
  - transcutaneous, treatment of reflex sympathetic dystrophy in a 6-year-old 1977;56:438
- nuclear magnetic resonance (letter) 1984;63:622
- obstetric side brace (letter) 1984;63:1046
- operating tables, neurosurgical operations, patient with lateral position 1980;59:503
- oxygen analyzers, disconnections (letter) 1984;63:464
- pacemakers
  - anesthesia 1976;55:626
  - electrocautery-induced (letter) 1984;63:541
- PEEP device, for a manual bag ventilator (brief reports) 1976;55:745
- plethysmograph, photoelectric digital 1975;54:289
- pumps
  - aid to rapid infusion 1979;58:155
  - hypotension caused by failure of pump 1979;58:250
  - pressurized system for fluid resuscitation 1984;63:779
- resuscitation bags 1975;54:133
- sphygmomanometer, possibly related to ulnar nerve palsy 1981;60:687
- stethoscope, inexpensive precordial (correspondence) 1978;57:598
- stopcocks, contamination 1979;58:141
- stylets (correspondence) 1977;56:325
- stylets, plastic covered solid copper wire (brief reports) 1976;55:150
- syringes, epidural anesthesia (letter) 1980;59:805
- tracheobronchial suction 1976;55:290
- transducers 1983;62:112
  - pressure domes containing diaphragm, laboratory evaluation of 1978;57:67
- tubes, endobronchial, double-lumen tube adapter 1980;59:507
- tubes, endotracheal
  - airway management of children with facial burns 1981;60:116
  - airway obstruction management, prone position 1980;59:700
  - anode hazards 1975;54:710
  - armored 1975;54:756
  - armored, hazard associated with (correspondence) 1978;57:381
  - Carden (brief reports) 1976;55:882
  - collapse due to overinflation of high-compliance cuffs 1977;56:731
  - complication 1980;59:215
  - complications 1984;63:457
  - cuff difficult extubation (brief reports) 1976;55:876
  - cuff herniation of, as cause of airway obstruction 1978;57:114
  - defective disposable, (brief reports) 1976;55:437
  - extubation (brief reports) 1976;55:876
  - flammability of during carbon dioxide

    - laser surgery 1981;60:885
  - hazard alert 1980;59:519
  - laser surgery of the airway 1980;59:789
  - (letter) 1984;63:701
  - method for verifying placement 1977;56:123
  - passed through bite block (letter) 1981;60:66
  - pediatrics (brief reports) 1975;54:273
  - questions and answers 1975;54:715
  - Rusch armored 1975;54:756
  - securing in children 1981;60:224
  - significance of $P_{CO_2}$ (brief reports) 1976;55:595
  - standard nomenclature (letter) 1980;59:517
  - swallowing by newborn (letter) 1979;58:156
  - wire-reinforced, complication associated with 1979;58:152
- tubes, nasogastric
  - Magill tube for inserting (brief reports) 1975;54:156
  - simple method for inserting (brief reports) 1976;55:303
- tubes tracheal, cuffed, physical and behavioral characteristics 1982;61:36
- tubes, tracheal (letter) 1982;61:161, 623
- valves
  - airway obstruction by breakdown of non-rebreathing valve 1981;60:529
  - detecting anesthesia circuit dysfunction 1984;63:536
  - failure of (letter) 1981;60:843
  - misassembly and use of resuscitation bag (letter) 1981;60:66
- vaporizers
  - (abstract) 1984;63:189
  - accuracy and nitrous oxide 1982;61:938
  - bottle adaptors for (letter) 1979;58:156
  - effect of nitrous oxide solubility (letter) 1983;62:956
  - enflurane concentrations increased by nitrous oxide delivered by 1979;58:30(letter) 1979;58:440, 441
  - Fluotec Mark III, gas leak 1979;58:239
  - for ether (correspondence) 1978;57:147
  - gas loss from Ohio modulus vaporizer selector-interlock valve (letter) 1983;62:1052
  - hazard (letter) 1980;59:805
  - inadvertent change of anesthetics 1982;61:53
  - isoflurane, evaluation 1982;61:457
  - leakage when turned off 1977;56:793
  - loss of anesthetic gases (letter) 1983;62:369
  - low-flow and closed-circuit anesthesia 1980;59:359
  - malfunctioning halothane vaporizer (letter) 1981;60:121
  - nitrous oxide (letter) 1980;59:808
  - possible hazard with use of Ohio Ethrane 1980;59:65
  - volatile anesthetics 1979;58:322
- ventilators 1983;62:122
  - (brief reports) 1976;55:879
  - correction for gas compression 1980;59:488
  - dilution of anesthetic detected by oxygen analyzer 1978;57:491
  - fleuric high frequency jet 1982;61:138
  - fresh gas flow effects on minute volume (letter) 1984;63:619
  - front panel cover for Frazer-Harlake ventilator (letter) 1983;62:619
  - inexpensive portable positive end-expiratory pressure system 1979;58:53
  - manual bag, PEEP device (brief reports) 1976;55:745
  - mobile respiratory assistor, for neonatal transport 1978;57:729
  - pediatrics 1976;55:769
  - portable system for critically ill patients 1981;60:760
  - silent 1982;61:713
- video-stethoscope, continuous bilateral lung ventilation during anesthesia 1983;62:586
- viscosity 1980;59:192
- warmers, for antiseptic skin preparation solutions 1977;56:124
- Y-piece, durability of (letter) 1981;60:912

**Esophagus,** see Gastrointestinal tract
**Ethanol,** see Alcohol
**Ethics**
- duplication and fragmentation in publications (letters) 1982;61:1024, 1025
- research, hazards of ketamine in ischemic heart disease (letter) 1983;62:1044

**Ethylene oxide,** see Sterilization
**Etidocaine,** see Anesthetics, local
**Etomidate,** see
- Anesthetics, intravenous
- Induction, anesthesia

**Etoxadrol hydrochloride,** see Anesthetics, intravenous
**Evoked potentials,** see
- Brain, monitoring
- Monitoring

**Extradural,** see Anesthetic techniques, epidural
**Extubation,** see Anesthetic techniques
**Eye**
- abducens palsy, postural puncture headache 1982;61:948
- blindness
  - following attempted stellate ganglion block 1981;60:689
  - transient, following intravenous atropine 1977;56:872
- blepharoplasty and rhytidectomy 1976;55:165
- corneal abrasion
  - anesthesia 1975;54:465
  - during general anesthesia 1977;56:363
- electroshock therapy, intraocular pressure 1975;54:479
- emergence phenomena
  - ketamine 1975;54:312
- glaucoma, pre- and post-anesthetic use of atropine (questions and answers) 1976;55:460
- intraocular pressure
  - anesthesia for electroshock therapy 1975;54:479
  - during enflurane and neurolept anesthesia in adult ophthalmic surgery 1980;59:50
  - effects of alcuronium 1983;62:521
  - enflurane 1975;54:212
  - ketamine in children 1976;55:773
  - thiopental and succinylcholine 1975;54:471
  - timolol-induced bradycardia 1980;59:301
- intraocular pressure (letter) 1984;63:543
- pupil
  - racial mydriatic response to belladonna premedication 1978;57:572
  - size during reversal of muscle relaxants 1980;59:615
- reflexes, oculocardiac, in eye-surgery anesthesia 1977;56:333
- retrolental fibroplasia
  - factors influencing development of (letter) 1981;60:539
  - multifactorial disease 1981;60:109
- tearing, effects of general anesthesia on basal production 1977;56:35
- vitrectomy 1975;54:58

**Fazadinium,** see Neuromuscular relaxants
**Femoral,** see
- Anatomy
- Anesthetic techniques, regional

**Fenoprofen,** see Analgesics
**Fentanyl,** see
- Analgesics, narcotic
- Anesthetics, intravenous

**Fetus,** see
- Anesthesia
- Pregnancy
- Toxicity
- Uterus

**Fiberoptic,** see Equipment
**Fibrillation,** see Heart, arrhythmias
**Filters,** see
- Blood
- Equipment, transfusion
- Transfusion

**Fire,** see
- Anesthetic techniques, laser surgery
- Complications
- Electrical systems

**Fluid balance**
- colloid or crystalloid (letter) 1981;60:228

- **Fluid balance**—*continued*
  - hypertonic solutions, hypotension and respiratory distress 1979;58:42
  - inflammatory potential of foreign particulates in parenteral drugs 1977;56:422
  - obstetric
    - maternal and fetal effects of prophylactic hydration before epidural anesthesia 1983;62:673
    - prehydration before epidural anesthesia 1984;63:69
  - volume expansion in interstitial lung diseases 1979;58:13
- **Fluoride,** see Ions
- **Flurothyl,** see Anesthetics, volatile
- **Fructose-1, 6-diphosphatase,** see
  - Enzymes
  - Genetic factors
- **Furosemide,** see
  - Kidney, diuretics
  - Neuromuscular relaxants
- **Gases, nonanesthetic**
  - helium, epinephrine-induced arrhythmias during halothane anesthesia 1982;61:414
  - nitrogen, epinephrine-induced arrhythmias during halothane anesthesia 1982;61:414
  - nitrogen, oxygenation during intubation 1981;60:313
  - nitrous oxide, epinephrine-induced arrhythmias during halothane anesthesia 1982;61:414
- **Gastrointestinal tract**
  - antacids
    - cimetidine (abstract) 1984;63:257
    - cimetidine, effects on gastric volume and pH 1984;63:599
    - citrate (abstract) 1984;63:205
    - effect of metoclopramide on gastric contents after sodium citrate 1984;63:841
    - in gastric acid neutralization 1984;63:325
    - radio pills for measurement of duration of action (letter) 1983;62:368
  - biliary tract, naloxone reversal of morphine-induced colic 1980;59:619
  - esophagus
    - domperidone antagonizes atropine effects 1980;59:921
    - effects of pancuronium and atracurium 1984;63:65
    - intubation (correspondence) 1978;57:288
    - sphincter tone during reversal of neuromuscular blockade by atropine and neostigmine 1978;57:171
    - spinal anesthesia 1983;62:606
  - intestine
    - effect of neostigmine (questions and answers) 1977;56:594
    - effect of nitrous oxide on bowel gases 1979;58:405
  - jejunoileal shunt
    - anesthesia for 1975;54:65
  - metoclopramide
    - (abstract) 1984;63:264
    - effect on gastric contents after sodium citrate 1984;63:841
    - effect on gastric fluid pH and volume 1984;63:1014
    - effects on gastric volume and pH 1984;63:599
  - stomach
    - antacids and glycopyrrolate (correspondence) 1978;57:145
    - bicitra (letter) 1982;61:801
    - cimetidine and related drugs 1982;61:595
    - cimetidine, effect on gastric fluid pH and volume 1984;63:1014
    - cimetidine for prophylaxis of aspiration pneumonitis 1979;58:426
    - comparison (abstract) 1982;61:167
    - control of acidity by glycopyrrolate premedication in parturient 1977;56:642
    - function (letter) 1980;59:807
    - gastric acid aspiration, two anesthetic techniques 1980;59:862
    - gastric acidity and glycopyrrolate premedication (letter) 1979;58:157
    - gastric distension during resuscitation (letter) 1981;60:619
    - gastric fluid volume after anesthesia 1980;59:287
    - gastric levels of meperidine in surgical patients 1979;58:88
    - gastric secretions in obesity 1981;60:37
    - nasogastric tube insertion (brief reports) 1975;54:156
    - nasogastric tube insertion, simple method (brief reports) 1976;55:303
    - neonatal pH 1978;57:98
    - nonparticulate (letter) 1982;61:801
    - pH, cimetidine as an oral antacid in obstetric anesthesia 1983;62:720
    - pH, in patients receiving cimetidine 1978;57:675
    - pH, in patients receiving sodium citrate 1981;60:521
    - pH and volume
    - effect of cimetidine 1979;58:183
    - effects of preanesthetic glycopyrrolates and cimetidine 1984;63:40
    - effects of ranitidine and metoclopramide 1984;63:903
    - preanesthetic cimetidine 1979;58:309
    - ranitidine and Mendelson's syndrome 1982;61:130
    - silent gastric regurgitation 1981;60:655
    - sodium citrate (abstract) 1982;61:220
    - sodium citrate and gastric pH 1981;60:521
    - sodium citrate, duration of action (letter) 1982;61:624
  - surgery, gastrointestinal, circulatory responses and concentrations 1976;55:388
- **Genetic factors** 1984;63:35
  - cholinesterase, and increased sensitivity to succinylcholine 1978;57:422
  - fructose-1, 6-diphosphatase, deficiency, anesthetic management of patient with 1978;57:503
  - malignant hyperthermia, spectrum of susceptibility 1983;62:545
  - potencies of nitrous oxide in mice bred for resistance or susceptibility 1981;60:646
  - pseudocholinesterase, succinylcholine-induced fasciculation as indicator of atypical 1984;63:869
  - race, mydriatic response to belladonna premedication 1978;57:572
- **Gentamicin,** see Antibiotics
- **Geriatric,** see
  - Age factors
  - Anesthesia, geriatric
- **Glaucoma,** see Eye
- **Glomus bodies,** see Anatomy
- **Glucagon,** see
  - Hormones
  - Metabolism
- **Glucose,** see
  - Blood
  - Metabolism
- **Glycopyrrolate,** see
  - Parasympathetic nervous system
  - Premedication
- **Growth hormone,** see Hormones
- **Hallermann-Streiff syndrome,** see
  - Complications
- **Head straps,** see Equipment
- **Heart**
  - adenylate cyclase, regulation with halothane 1984;63:285
  - anesthesia for patients post infarction 1976;55:640
  - arrhythmia
    - aminophylline during halothane anesthesia, experimental animals 1980;59:410
    - aminophylline, interaction with halothane, multiform ventricular tachycardia due to 1978;57:740
    - amitriptyline therapy increases electrocardiographic changes during neuromuscular blockade reversal 1978;57:77
    - antiarrhythmic action of adenosine triphosphate 1982;61:423
    - arrhythmic doses of epinephrine and dopamine during halothane, enflurane, methoxyflurane, and fluroxene anesthesia 1977;56:207
    - arrhythmic effects of stellate ganglion block on the idiopathic prolongation of the Q-T interval 1976;55:782

  asphyxial challenge in chronically hypokalemic dogs 1983;62:991
  atrial arrhythmias and digoxin 1981;60:302
  correlation with $\alpha$-adrenergic responsiveness 1984;63:297
  effect of isoflurane following aminophylline 1983;62:568
  effects of stellate ganglion block on the idiopathic prolongation of the Q-T interval 1976;55:782
  epinephrine-induced, during enflurane anesthesia: protection from lidocaine 1978;57:547
  epinephrine-induced during halothane anesthesia 1982;61:414
  exogenous prostaglandins and prostaglandin synthesis inhibition during halothane–$O_2$ anesthesia 1979;58:401
  epinephrine injection 1975;54:468
  fibrillation, induced during cardiac surgery 1984;63:743
  fibrillation, ventricular, comparison of THAM and sodium bicarbonate in resuscitation 1977;56:38
  following epinephrine injection 1975;54:468
  following reversal of neuromuscular blocking agents in geriatric patients 1978;57:186
  following succinylcholine, atropine 1975;54:705
  halothane-induced cardiac arrhythmias 1981;60:517
  hypotension following bretylium tosylate 1979;58:516
  low-energy ventricular defibrillation during cardiac surgery (abstract) 1983;62:269
  mechanical hyperventilation effect with pentobarbital 1980;59:839
  safety of enflurane following administration of aminophylline 1981;60:871
  ventricular, halothane–epinephrine induced after imipramine 1984;63:825
assist devices, left heart, postperfusion low cardiac output 1977;56:402
asystole
  after single dose of succinylcholine 1978;57:135
  persistent electromechanical arrest following cardioplegic and glucose-insulin-potassium solutions 1980;59:69
atria, chronotropic effects of volatile inhalation anesthetics 1977;56:173
block
  and artificial cardiac pacemakers 1976;55:626
  anesthesia 1976;55:626
  anesthesia and complete congenital block 1981;60:906
  coincidential fetal and maternal 1981;60:59
  congenital, anesthetic management of, in childhood 1979;58:334
  congenital complete (letter) 1980;59:81
  left bundle branch, during anesthesia 1980;59:628
blood flow
  cardiovascular effects of morphine 1982;61:109
  effect of hypocapria 1984;63:991
  effects of isoflurane and halothane anesthesia 1976;55:135, 1984;63:557
  ischemia caused by mediastinal chest tube suction 1980;59:386
  myocardial clinical anesthesia 1980;59:229
cardiac output 1984;63:963
  effect of halothane and pentobarbital on dispersion of indicator particles in central circulation 1977;56:68
  effects of ventilatory pattern, intrapleural pressure, and 1977;56:88
  estimation by $CO_2$ breathing method (abstract) 1980;59:555
  isoflurane effect with or without 50% nitrous oxide 1983;62:499
  myocardial function, cardiovascular effects of enflurane during controlled ventilation 1978;57:619
  myocardial function, effects of enflurane during spontaneous ventilation 1978;57:610
cardiac tamponade, effects of hypo-, normo-, and hypercarbia 1983;62:181
catheterization
  acute respiratory distress complication 1980;59:442
  central venous pressure, catheter positioning (brief reports) 1975;54:696
  ECG-guided placement 1984;63:953
  hydromediastinum after 1980;59:159
  intracardiac knotting of balloon-tipped catheter 1980;59:217
  vascular cannulation (abstract) 1980;59:563
conduction
  effect of halothane on canine intracardiac impulse, during sinus rhythm, antiarrhythmic anesthetic action 1977;56:187
  effects of thoracic epidural analgesia 1984;63:817
  halothane anesthesia 1980;59:327
  halothane effects, conductivity of AV node, and His-Purkinje system 1977;56:378
congenital defects, effects of ketamine on congenital heart disease 1984;63:895
contractility
  action of thiopental and halothane 1984;63:313
  defining myocardial depression (abstract) 1982;61:174
  diazepam and fentanyl—negative inotropic effect 1984;63:97
  effects of diethyl ether and nitrous oxide 1984;63:451
  effects of etomidate and thiopental 1983;62:961
  effects of fentanyl and nitrous oxide 1984;63:47
  negative inotropic effect of halothane in rabbit papillary muscle 1982;61:403
  negative inotropic effect of protamine sulfate 1980;59:100
  protamine toxicity in isolated heart tissue 1984;63:1111
  following regional anesthesia in patients undergoing carotid endarterectomy (abstract) 1983;62:279
  myocardial infarction following anesthesia (abstract) 1981;60:271
digitalis tolerance
  effect of enflurane, isoflurane, fluroxene, methoxyflurane and diethyl ether anesthesia 1976;55:360
  effects of ketamine and Innovar 1975;54:106
digoxin
  hypokalemic dogs treated with, and intravenous potassium chloride 1978;57:108
  peripheral vascular and direct cardiac effects 1980;59:11
dobutamine, myocardial metabolism 1982;61:917
dopamine, arrhythmic doses of, and epinephrine, during halothane, enflurane, methoxyflurane, and fluroxene anesthesia 1977;56:207
drugs, cardiac supportive care 1976;55:633
echocardiography
  (abstract) 1984;63:194
  myocardial function, analysis during halothane anesthesia 1979;58:23
Eisenmenger syndrome, general anesthesia in presence of 1977;56:543
electrocardiography
  $CB_5$ lead monitoring 1981;60:849
  continuous beat-to-beat microcomputer analysis and quantification of the intraoperative ECG (abstract) 1983;62:273
  diagnostic value of $V_5$ precordial lead 1978;57:364
  esophageal, intraoperative monitoring 1982;61:781
  intraoperative esophageal cardiokymogram (abstract) 1983;62:256
  intravascular (letter) 1982;61:884
  precordial ECG lead, chest operations (brief reports) 1976;55:740

**Heart**—*continued*
  electrocardiography—*continued*
    rechargeable monitor (Tektronix) (questions and answers) 1976;55:613
  emergency surgery, during acute myocardial infarction (case history) 1975;54:267
  epinephrine, arrhythmic doses of, and dopamine, during halothane, enflurane, methoxyflurane, and fluroxene anesthesia 1977;56:207
  evaluation preoperative and preparation of the cardiac 1976;55:618
  failure, associated with hypocalcemia 1976;55:34
  function, nitrous oxide, responses to, during halothane anesthesia 1978;57:84
  halothane, hemodynamic responses to nifedipine during anesthesia 1983;62:903
  herniation correspondence 1978;57:747
  hypocarbia, effect on myocardial function 1984;63:991
  implantation, artificial 1976;55:560
  infarction, following local anesthesia for ophthalmic surgery 1980;59:257
  ischemia
    early diagnosis using the pulmonary arterial catheter 1981;60:789
    effects of isoflurane and halothane 1984;63:635
    use of electrocardiography 1984;63:343
    vasospastic angina after calcium injection 1984;63:1124
  isoproterenol
    beta-adrenoceptor responsiveness during anesthesia (abstract) 1983;62:255
    cardiovascular and respiratory effects, artificial heart implantation 1976;55:560
  massage
    leg-heel vs standard arm-hand method of external cardiac compression 1979;58:170
    propranolol and, effect on halothane MAC in dogs 1976;55:383
  metabolism
    after acute $\beta$-adrenergic blockade (letter) 1984;63:540
    fentanyl effects during experimental ischemia 1980;59:644
    protamine sulfate and 1982;61:247
  metoprolol, long-term therapy and neuroleptanesthesia in coronary artery surgery 1983;62:380
  mitral valve, prolapse 1980;59:379
  monitoring, hemodynamic tracking system 1980;59:169
  morphine anesthesia, urine norepinephrine excretion 1975;54:509
  myocardial function
    acetate fails to reverse depression in dogs anesthetized with halothane 1978;57:395
    afterload reduction and preload augmentation 1980;59:737
    analysis of regulation 1977;56:761
    anesthesia (abstract) 1980;59:564
    droperidol and ketamine 1983;62:193
    embolism 1984;63:429
    halothane 1984;63:731
    halothane and enflurane 1980;59:240
    halothane-induced depression, asynergic contraction 1980;59:178
    hyperkalemia and cardiovascular collapse after verapamil and dantrolene administration 1984;63:473
    isoflurane and halothane 1976;55:135, 1984;63:557
    mannitol, effects on blood volume and central hemodynamics during cerebral aneurysm surgery 1983;62:875
    neuromuscular relaxants on canine heart muscle 1980;59:717
    nitroglycerin 1982;61:927
    nitroprusside and mitral stenosis 1980;59:662
    nitrous oxide on, during meperidine infusion 1977;56:836
    ventricular dysfunction (abstract) 1980;59:550
    ventricular performance (abstract) 1984;63:217
  myocardial infarction
    cardiac electrical activity after myocardial preservation with cardioplegia solution (abstract) 1983;62:269
    influence of lidocaine and bupivacaine on atria 1984;63:01
  myocardial metabolism, effects of droperidol and ketamine 1983;62:193
  nadolol 1984;63:365
  nifedipine, hemodynamic effects during halothane anesthesia 1983;62:903
  nifedipine–halothane (letter) 1984;63:622
  nitrous oxide, response to exposure 1980;59:93
  ouabain
    general anesthetic agents, and aldosterone effect on striated muscle contraction 1976;55:409
    morphine antagonism 1975;54:787
    tolerance, effect of enflurane, isoflurane, fluroxene, methoxyflurane, and diethyl ether anesthesia 1976;55:360
  oxygen consumption
    afterload changes during halothane anesthesia 1980;59:233
    anesthesia, coronary patients (abstract) 1982;61:204
    during prolonged anesthesia (abstract) 1983;62:280
    during prolonged halothane anesthesia 1983;62:788
    hemodynamics of intravenous nitroglycerin 1982;61:927
    myocardial, with halothane and morphine anesthesia 1982;61:979
    sodium nitroprusside effects during halothane anesthesia 1980;59:835
  pacemakers
    anesthesia 1976;55:626
    artificial cardiac, with heart block 1976;55:626
    electrocautery-induced (letter) 1984;63:541
    electrocautery-induced reprogramming using a precordial magnet 1983;62:609
  pediatric, phagocytosis 1975;54:501
  pericardium
    anesthesia and pericardial disease 1983;62:431
    severe tachycardia 1982;61:384
  pharmacology, calcium entry blockers 1984;63:515
  pneumocardiography
    automated measurement and frequency analysis 1978;57:647
    determinants and genesis of 1978;57:653
  problems with aspirin intolerance 1975;54:376
  propranolol 1976;55:01
    anesthetics and 1977;56:283
    block after coronary artery bypass surgery 1984;63:515
    hemodynamic effects of metocurine in patients with coronary artery disease receiving 1977;56:255
    hemodynamics and myocardial metabolism (letter) 1984;63:540
  pulse rate
    baroreflex control by epidural anesthesia 1983;62:815
    chronotropic effects of volatile inhalation anesthetics 1977;56:173
    pentobarbital–morphine antagonism 1984;63:669
  rapid induction in combat casualties 1976;55:74
  rate, effect of atropine 1975;54:262
  rate of recovery in rats 1975;54:96
  rate-pressure product, clinical anesthesia 1980;59:229
  receptors 1981;60:40
  resuscitation
    advanced CPR 1982;61:629, (letter) 1983;62:541
    cerebral blood flow during 1981;60:73
    interposed abdominal compression 1982;61:645
    new concepts in 1981;60:100
  sarcoplasmic reticulum, calcium transport 1981;60:390
  systolic time intervals, effect of halothane on 1977;56:522
  tamponade, transmural myocardial pressures (letter) 1984;63:93
  transplant donor death, physician liability (physician and the law) 1976;55:611

- valvular disease, effects of calcium chloride 1984;63:723
- ventricles, effect of methoxyflurane on automaticity 1977;56:194
- verapamil
  - (abstract) 1984;63:230, 231
  - during coronary artery bypass graft surgery 1983;62:821
  - effect on vecuronium neuromuscular blockade 1984;63:155
  - for treatment of arrhythmias after cardiopulmonary bypass 1984;63:460
  - hemodynamic interactions with halothane 1984;63:791
  - isoflurane interactions (abstract) 1982;61:194
  - neuromuscular and electrocardiographic responses 1983;62:50

**Helium,** see Gases, nonanesthetic

**Hematoma,** see Complications

**Hemiplegia,** see Complications, paralysis

**Hemoglobin,** see Blood

**Hemophilia,** see Blood, coagulation

**Hemorrhage**
- effect of anesthetics 1981;60:481
- pulmonary, during pulmonary embolectomy 1976;55:182

**Heparin,** see Blood, coagulation

**Hepatitis,** see Liver

**Hepatocytes,** see Liver

**Hepatotoxicity,** see Liver

**Heroin,** see Analgesics

**Hexobarbital,** see
- Anesthetics, intravenous
- Hypnotics, barbiturates

**Hiccups,** see Complications

**High-frequency ventilation,** see Ventilation

**Histamine**
- antagonists, effects on adrenergic function in canine saphenous veins 1983;62:21
- cimetidine
  - effect on gastric secretions in obesity 1981;60:37
  - pre-anesthetic, and gastric pH 1979;58:309
  - used as an oral antacid in obstetric anesthesia 1983;62:720
- hormonal effect of diazepam–fentanyl during coronary artery bypass surgery 1983;62:881
- inhibition, gastric fluid pH in patients receiving cimetidine 1978;57:675
- ranitidine, Mendelson's syndrome 1982;61:130

**History**
- anesthesia, development of surgery and (1846–1896) 1979;58:05
- Dr. Arthur Ernest Guedel 1975;54:442
- Dr. August Karl Gustav Bier 1975;54:322
- Dr. Carl Koller 1975;54:247
- drug inhalation 1980;59:140
- Howard Wilcox Haggard 1975;54:654
- ideas in anesthesia 1976;55:467
- introduction of surgery and development of anesthesia (editorial) 1979;58:04
- obstetric anesthesia, the first experiment (letter) 1983;62:1136
- pollution, cause for concern 55 years ago (correspondence) 1978;57:516
- publications, anesthesia and 1980;59:01
- Rudolph Matas 1975;54:29
- surgery, anesthesia and development of (1846–1896) 1979;58:05
- William T. G. Morton (letter) 1979;58:260
- Yandell Henderson 1975;54:806

**Hodgkin's disease,** see Complications

**Homocystinuria,** see Complications

**Hormones**
- adrenal
  - cortical, for sciatica 1978;57:313
  - epidural treatment of acute herniated nucleus pulposus 1977;56:862
  - steroids and anesthesia (correspondence) 1978;57:379
- aldosterone, general anesthetic agents and ouabain, striated muscle contraction 1976;55:409
- aldosterone, renal function and stress response 1981;60:552
- antidiuretic, influence of epidural fentanyl on ADH levels 1983;62:727
- antidiuretic hormone, responses after sufentanil and alfentanil anesthesia 1982;61:434
- antidiuretics, effect of fentanyl on arginine vasopressin and cortisol secretion 1984;63:25
- corticosteroids
  - effect of fentanyl on arginine vasopressin and cortisol secretion 1984;63:25
  - effect on nerves and meninges 1980;59:610
- glucagon
  - biliary spasm and fentanyl 1981;60:638
  - narcotic-induced choledochoduodenal sphincter spasm 1980;59:946
  - plasma during spinal anesthesia and surgery in a glucagon-deficient patient 1983;62:846
- growth hormone, responses after sufentanil and alfentanil anesthesia 1982;61:434
- insulin
  - artificial beta cell during anesthesia 1980;59:950
  - effects of enflurane on release of 1981;60:878
  - maternal-fetal glucose homeostasis 1982;61:32
- prolactin, cholinergic action of thiopental 1981;60:310
- prostaglandins
  - epinephrine-induced arrhythmias in dogs during halothane–$O_2$ anesthesia 1979;58:401
  - uterine rupture (letter) 1983;62:1046
- renin, renal function and stress response 1981;60:552
- thyroid
  - anesthesia and hypothyroidism 1982;61:371
  - anesthesia for untreated hypothyroidism 1977;56:299
  - malignant hyperthyroidism or malignant hyperthermia 1981;60:613
- thyroid stimulating, cholinergic action of thiopental 1981;60:310
- vasopressin, renal function and stress response 1981;60:552

**Horner's syndrome,** see Sympathetic nervous system entries for stellate ganglion

**Humidification**
- adult body temperature during general anesthesia 1981;60:736
- anesthesia circuits, Pall bacterial filter 1984;63:566
- anesthetic gases
  - effect on temperature after cardiopulmonary bypass surgery 1984;63:1106
  - heated water humidifier with rotating wick 1979;58:244
  - (letter) 1981;60:694
  - modified circle system 1979;58:216
- anesthetic systems 1975;54:50
- carbon dioxide absorption, in infant circuit 1978;57:307
- Columbia pediatric circle (brief reports) 1976;55:877
- contamination, by bacteria, in heated nebulizer 1978;57:191
- CPRAM, children and adults (abstract) 1980;59:556
- heated, maintenance of body temperature 1976;55:710
- immersion heater, inspired air temperature 1976;55:331
- improvement of by use of percolator vaporizer 1981;60:146
- indications and hazards, in respiratory therapy 1975;54:444
- jet ventilation, coaxial jet ventilation catheter 1982;61:689
- nonrebreathing system 1975;54:271
- operating rooms (questions and answers) 1976;55:134

**Hydralazine,** see Anesthetic techniques, hypotensive

**Hydromorphone,** see Analgesics

**Hydroxyzine,** see
- Ataractics
- Hypnotics

**Hyperbaria**
- oxygen, hepatoprotective effect during halothane anesthesia 1978;57:481
- pressure reversal
  - and isoflurane 1977;56:97
  - nonlinear antagonism of anesthesia 1979;58:19

**Hypercapnia,** see
  Carbon dioxide
  Acid-base equilibrium
**Hypercarbia,** see
  Carbon dioxide
  Acid-base equilibrium
**Hyperoxia,** see Oxygen
**Hyperpyrexia,** see
  Hyperthermia
**Hypertension,** see
  Blood pressure
  Complications
**Hyperthermia**
  hypoxic survival, influence of alone or in combination with pentobarbital or phenytoin 1981;60:867
  malignant 1983;62:115, 119
    (abstract) 1984;63:193
    associated with enflurane anesthesia 1975;54:47
    awake episodes, correction by Dantrolene 1980;59:377
    Burkitt's lymphoma 1980;59:514, (letter) 1980;59:955
    $Ca^{2+}$ dependence during calcium uptake by isolated sarcoplasmic reticulum 1981;60:492
    case report 1980;59:220
    contracture tests for susceptibility 1983;62:415
    creatine phosphokinase activity 1975;54:536
    editorial 1980;59:321
    enflurane anesthesia 1975;54:47
    halothane-induced biochemical defect in muscle 1980;59:250
    halothane-succinylcholine induced masseter spasm 1984;63:693
    in six-month-old infant 1978;57:262
    intraoperative crisis in two children with undifferentiated lymphoma 1978;57:511
    isoenzymes of creative phosphokinase in serum 1976;55:797
    isoflurane and (letter) 1982;61:711, 712
    isometric twitch and tetanus response 1975;54:527
    (letter) 1984;63:91
    massive myoglobinuria 1976;55:680
    mistaken for hyperthyroidism 1981;60:613
    muscle contractures and adenosine triphosphate depletion as tests for 1979;58:367
    neuroleptic malignant syndrome 1983;62:848
    pancuronium and (letter) 1980;59:889
    phosphorylase activity (letter) 1984;63:88
    phosphorylase ratio and susceptibility 1983;62:324
    preanesthetic evaluation and management 1976;55:643
    skeletal muscle mitochondria in 1979;58:76
    spectrum of susceptibility 1983;62:545
    syndrome (correspondence) 1977;56:466
    tourniquet test (abstract) 1981;60:256
    treatment with calcium channel blocker (letter) 1983;62:861
    variations in onset 1981;60:499
  malignant pyrexia
    failure of lidocaine to trigger 1979;58:99
    management in an infant 1979;58:33
**Hypnosis**
  monitoring intraoperative spinal cord function 1976;55:42
**Hypnotics**
  barbiturates
    cardiovascular effects (abstract) 1980;59:559
    effects on cardiac acceleration response to noxious stimulation 1984;63:669
    induced coma (abstract) 1981;60:247
    influence in hypoxic survival in combination with hypothermia or hyperthermia 1981;60:867
    pentobarbital
      and halothane, effect on dispersion of indicator particles in central circulation of dog 1977;56:68
      induced coma (abstract) 1981;60:247
      influence on hypoxic survival in combination with hypothermia or hyperthermia 1981;60:867
      versus lorazepam premedication 1977;56:489
    potency and nitrous oxide susceptibility 1984;63:35
    tolerance 1981;60:137
  benzodiazepines
    atropine in physostigmine reversal of diazepam (letters) 1980;59:459
  cardiovascular effects, coronary artery disease (abstract) 1982;61:217
  catecholamine release with morphine and diazepam 1981;60:406
  circulatory responses 1983;62:135
  diazepam
    and pentazocine supplementing local analgesia 1976;55:177
    and succinylcholine-induced muscle pains 1978;57:295
    antagonized by aminophylline 1984;63:900
    as surgical premedicant 1977;56:211
    comparison with droperidol and hydroxyzine as premedication 1977;56:496
    dental anesthesia 1980;59:775
    droperidol, and hydroxyzine changes in airway resistance 1976;55:18
    effect on memory and learning 1979;58:452
    effects of age and sex on bioavailability 1983;62:01
    effects on evoked electrospinogram and evoked electromyogram 1981;60:197
    effects on succinylcholine-induced muscle pain 1979;58:314
    functional residual capacity and ventilation distribution (abstract) 1982;61:209
    hemodynamic responses to anesthetic induction in patients with ischemic heart disease 1981;60:802
    in patients with severe burns 1983;62:293
    induction agents and renal hemodynamics 1982;61:853
    influence on serum protein binding of bupivacaine 1984;63:980
    interaction with fentanyl during coronary artery surgery 1983;62:881
    negative inotropic effect 1984;63:97
    neonatal electroencephalographic patterns as affected by maternal administration 1978;57:303
    or droperidol, respiratory function following premedication with 1978;57:695
    patients with coronary artery disease 1980;59:438
    physostigmine-atropine solution failure to reverse 1980;59:58
    physostigmine reversal of depression induced by 1977;56:348
    plasma levels 1975;54:173
    prevention of succinylcholine-induced fasciculations 1980;59:932
    protects mice from local anesthetic convulsions and death 1981;60:385
    reversal of physostigmine (letter) 1980;59:805
    thrombophlebitis after 1977;56:409
    with morphine, effect on awareness and dreams, nitrous oxide anesthesia 1976;55:702
  effect on recovery from anesthesia in rats 1975;54:97
  etomidate 1976;55:286
  hemodynamic effects, patients with coronary artery disease (abstract) 1980;59:551
  hepatic blood flow 1983;62:135
  hydroxyzine
    (abstract) 1984;63:176
    comparison of surgical premedicants 1984;63:571
    comparison with droperidol and

    diazepam as premedication 1977;56:496
    respiratory depression of intravenous hydroxyzine in man 1981;60:634
  lorazepam, comparison of surgical premedicants 1984;63:571
    failure to reverse clinical, psychomotor, or EEG effects 1983;62:679
    premedication, anxiety 1976;55:792
    protects mice from local anesthetic convulsions and death 1981;60:385
    versus pentobarbital premedication 1977;56:489
  midazolam 1983;62:75
    comparative cardiovascular effects (abstract) 1982;61:198
    delirium reversal, physostigmine 1975;54:607
    for anesthesia induction 1984;63:1116
    hemodynamic responses to anesthetic induction patients with ischemic heart disease 1981;60:802
    intramuscular premedication 1982;61:933
    oil emulsion (letter) 1982;61:544
    placental transfer 1984;63:31
    preanesthetic medication (abstract) 1983;62:256
    premedication, clinical evaluation, the effect on recall 1976;55:522
    premedication, evaluation of memory under regional anesthesia 1976;55:368
    premedication, lack of recall and relief of anxiety 1976;55:792
    protects mice from local anesthetic convulsions and death 1981;60:385
    respiratory depressant effects and lack of reversal with naloxone 1983;62:920
    thiopental hemodynamics and 1982;61:771
    ventilatory response to carbon dioxide (abstract) 1981;60:250
  pentobarbital, effects on cardiac acceleration response to noxious stimulation 1984;63:669
  physostigmine reversal of diazepam-induced depression 1977;56:348
**Hypobaria**
  anesthesia and altitude 1984;63:1097
**Hypocapnia,** see
  Acid-base equilibrium, alkalosis, respiratory
  Carbon dioxide
**Hypocarbia,** see
  Acid-base equilibrium, alkalosis, respiratory
  Carbon dioxide
**Hypophysectomy,** see
  Brain
  Surgery, neurologic
**Hypotension,** see
  Anesthetic techniques, hypotensive
  Blood pressure
  Complications
  Shock
**Hypothermia**
  during cystoscopy 1977;56:326
  hypoxic survival, influence of alone or in combination with pentobarbital or phenytoin 1981;60:867
  postoperative, relationship of age, anesthesia, and shivering to rewarming in adults 1981;60:746
  prevention, during cystoscopy in neonates (brief reports) 1976;55:592
  profound, heart defect surgery 1975;54:660
  rewarming, physicologic effects, possible application for neonatal cardiac surgery 1979;58:297
  with cardiac arrest, core rewarming by peritoneal irrigation in 1977;56:574
**Hypoxia**
  (abstract) 1984;63:195
  cerebrovascular response to, barbiturate coma (abstract) 1982;61:179
  detected by evoked potential monitoring 1981;60:437
  fluctuating, and pulmonary shunting following fatal head trauma 1977;56:129
  hepatic damage 1984;63:885
  hepatotoxicity, anesthetic induced 1983;62:140, 146, 155
  liver
    halothane-induced injury 1982;61:824
    hepatic injury 1982;61:820
  liver blood flow, effects of phenobarbital-pretreated rats during halothane anesthesia 1981;60:306
  pH, cerebral surface, changes during asphyxia, hypotension, and circulatory arrest 1977;56:817
  phenytoin, cardiac protection 1984;63:1021
  postoperative, early reversal 1976;55:822
  survival, influence of hypothermia or hyperthermia alone or in combination with pentobarbital or phenytoin 1981;60:867
  tissue pH monitoring during halothane or pentobarbital anesthesia (abstract) 1981;60:243
  see Oxygen
**Imipramine,** see Ataractics
**Induction**
  anesthesia
    alfentanil–thiopental comparison 1984;63:330
    circulatory changes 1976;55:77
    diazepam, hemodynamic responses in patients with ischemic heart disease 1981;60:802
    diffusion hyperoxia following preoxygenation 1977;56:59
    etomidate 1976;55:286, 730
    etomidate, cardiovascular and pulmonary responses in cardiac patients 1979;58:40
    etomidate, ultrashort-acting nonbarbiturate agent, for anesthetic induction 1976;55:286
    face mask and plasma norepinephrine levels (abstract) 1981;60:257
    feedback control of enflurane delivery 1983;62:836
    hemodynamic responses to midazolam and diazepam 1981;60:802
    increased cerebrospinal fluid pressure 1975;54:687
    influence of barbiturate, on circulatory responses to morphine 1977;56:615
    low-dose fentanyl preloading 1984;63:60
    midazolam 1983;62:75
    midazolam 1984;63:1116
    midazolam and thiopental hemodynamics 1982;61:771
    midazolam, hemodynamic responses in patients with ischemic heart disease 1981;60:802
    oxygenation during intubation 1981;60:313
    rapid, in combat casualties 1976;55:74
    RO 21-3981 for surgical premedication and 1978;57:01
    thiopental 1983;62:75
  enzymes, following surgery with halothane and neurolept anesthesia 1981;60:319
  see
    Biotransformation (drug)
    Pharmacokinetics
**Infarction, myocardial,** see Heart, coronary occlusion
**Infection**
  anesthesia, gas gangrene 1976;55:247
  bacteremia, cardiac arrest during anesthesia 1981;60:440
  hepatitis, prevalence in anesthesia personnel 1984;63:433, 738
  herpangina, in an anesthesiologist 1980;59:384
  modification of response, and anesthesia 1976;55:776
  peridural, potential for contamination of continuous catheters 1977;56:222
  pulmonary, defense mechanisms depressed by halothane 1979;58:505
**Infusors,** see Equipment
**Innovar,** see Anesthetics, intravenous

**Insulin,** see
- Hormones
- Metabolism

**Intensive care**
- pediatric, epiglottitis 1983;62:785
- postoperative, benefit of elective admission 1983;62:572

**Interactions (drug)**
- alcohol, influence on anesthetic requirements and acute toxicity 1980;59:826
- and anesthesia 1979;58:413
- antibiotics and relaxants neuromuscular effects 1979;58:107
- between *d*-tubocurarine, pancuronium, polymyxin B and neostigmine on neuromuscular function 1976;55:224
- diazepam, interaction with fentanyl during coronary artery surgery 1983;62:881
- drug-drug interaction (editor's choice) 1975;54:76
- drugs, cardiac supportive care 1976;55:633
- epinephrine, with enflurane, isoflurane and halothane in man 1976;55:709
- fentanyl, interaction with diazepam during coronary artery surgery 1983;62:881
- interaction of epinephrine with enflurane, isoflurane and halothane 1976;55:709
- ketamine, with neuromuscular blocking agents in phrenic nerve–hemidiaphragm preparation of rat 1978;57:238
- local anesthetics
  - duration of bupivacaine when mixed with chloroprocaine 1979;58:364
  - inhibit hydrolysis of chloroprocaine by human serum 1978;57:534
- local anesthetics and relaxants, at neuromuscular junction 1978;57:580
- neuromuscular 1980;59:678
- neuromuscular relaxants
  - pancuronium and metocurine in combination 1981;60:12
  - pancuronium and metocurine or *d*-tubocurarine 1980;59:604
  - protein binding effects 1983;62:160
- pancuronium–*d*-tubocurarine combination 1984;63:437
- see
  - Antagonists, narcotic
  - Antagonists, neuromuscular relaxants
  - Pharmacology

**Intercostal block,** see Anesthetic techniques, regional

**Intermittent mandatory ventilation,** see Ventilation

**Intermittent positive pressure breathing,** see Ventilation

**Interscalene block,** see Anesthetic techniques, regional, brachial plexus

**Intestine,** see Gastrointestinal tract

**Intracranial pressure,** see

**Intraocular pressure,** see Eye

**Intravenous anesthesia,** see
- Anesthetics, intravenous
- Anesthetic techniques

**Intravenous fluids,** see Fluid balance

**Intravenous regional anesthesia,** see Anesthetic techniques, regional

**Intubation**
- duration, early extubation vs prophylactic ventilation in high risk patients 1981;60:76
- endobronchial, for intraoperative protection of a single functioning lung 1976;55:340
- laryngeal, endotracheal sequelae 1975;54:767
- laryngeal sequelae, endotracheal intubation 1975;54:767
- laryngeal stenosis, in acromegaly 1976;55:57
- nasotracheal
  - lidocaine–phenylephrine as substitute for cocaine 1984;63:915
  - maxillary sinusitis (brief reports) 1976;55:885
- rapid, combat casualties 1976;55:74
- tracheal
  - (abstract) 1984;63:179, 188, 209, 229
  - airway resistance, under topical anesthesia 1980;59:270
  - alfentanil–thiopental comparison 1984;63:330
  - avoiding the trauma of (letter) 1981;60:618
  - awake 1975;54:323
  - blind intubation aid (letter) 1984;63:882
  - blood pressure, hypertension 1980;59:367
  - cell changes, prolonged cannulation 1980;59:759
  - circulatory responses with or without prior aerosolized lidocaine (abstract) 1983;62:288
  - complications, laryngeal pathology following long-term oral and nasal 1978;57:663
  - complications, low-dose fentanyl preloading 1984;63:60
  - complications, nitroprusside used to attenuate blood pressure response 1979;58:116
  - difficult intubation (letter) 1984;63:166
  - effects on blood pressure and heart rate 1983;62:951
  - effects on blood pressure and heart rate (abstract) 1983;62:278
  - fentanyl and postintubation hypertension 1982;61:680
  - fiberoptic laryngoscope guide and protector 1977;56:126
  - humoral response of hypertensive patients (abstracts) 1981;60:276
  - hypertension after (abstract) 1980;59:527
  - incidence and causes of failure 1983;62:692
  - laryngeal sequelae 1975;54:767
  - laryngoscopy and, circulatory response to, with or without prior oropharyngeal lidocaine 1977;56:618
  - method for blind oral, of trachea or esophagus 1977;56:866
  - myocardial consequences (abstract) 1983;62:249
  - new fiberoptic techniques for (letter) 1981;60:617
  - obstruction secondary to oral preoperative medication 1984;63:867
  - oxygenation during laryngoscopy intubation 1981;60:316
  - prolonged (brief reports) 1976;55:438
  - postintubation acute respiratory distress due to annular slough of laryngotracheal mucosa 1977;56:356
  - preextubation ventilatory measurements newborn and infant 1980;59:467
  - retrograde guide (letter) 1983;62:366
  - right upper lobe atelectasis 1983;62:851
  - use of kit as guide 1977;56:287
  - using fiberoptic stylet laryngoscope 1984;63:161
  - vocal cord paresis following (questions and answers) 1977;56:321
- tracheal and thiamylal-succinylcholine, circulatory changes in patients with coronary artery disease 1976;55:232
- translaryngeal, acute respiratory failure 1976;55:195

**Ions**
- bromine
  - electroencephalographic abnormalities following halothane 1978;57:244
  - prediction of halothane metabolism 1979;58:470
- calcium
  - (abstract) 1984;63:255
  - calcium transport by cardiac sarcoplasmic reticulum 1981;60:390
  - effect on the action of ketamine on cerebral and mesenteric arteries 1983;62:553
  - effects of verapamil on indirect muscle twitch responses 1983;62:827
  - effects on muscle contractility 1984;63:451
  - effects on regurgitant valvular heart disease 1984;63:723
  - hemodynamic responses to nifedipine during halothane anesthesia 1983;62:903

    - injection-induced vasospastic angina 1984;63:1124
    - transport, enflurane and isoflurane effects 1982;61:142
    - uptake by isolated sarcoplasmic reticulum 1981;60:492
    - verapamil, hemodynamic interactions with halothane 1984;63:791
  - citrate, effect on gastric fluid pH 1981;60:521
  - electrolyte disorders
    - carbon dioxide titration 1975;54:299
  - fluoride
    - in parturients and neonates following methoxyflurane analgesia 1977;56:646
    - levels in obese patients during and after enflurane 1979:58:409
  - magnesium, enhancing local nerve block 1984;63:111
  - potassium
    - acute hyperkalemia associated with massive blood replacement (letter) 1983;62:1044
    - acute hypocapneic hypokalemia 1977;56:786
    - cardiovascular responses to anoxic challenge (abstract) 1983;62:290
    - cardiovascular responses to asphyxial challenge in chronically hyperkalemic dogs 1983;62:991
    - changes in, and responses to neuromuscular blocking agents 1978;57:417
    - chronic hypokalemia (abstract) 1982;61:221
    - effect of succinylcholine in patients with infections 1983;62:327
    - effects of thiopental and succinylcholine 1984;63:1146
    - effects on anesthetic requirement, compared with brain sodium and osmolality 1978;57:404
    - efflux, influence of pancuronium 1976;55:474
    - hyperkalemia and cardiovascular collapse after verapamil and dantrolene administration 1984;63:473
    - hyperkalemia in recipients of kidneys preserved with 1980;59:283
    - hypokalemia associated with terbutaline 1980;59:917
    - hypokalemia management (questions and answers) 1976;55:276
    - in hypokalemic dogs treated with digoxin 1978;57:108
    - radiation and succinylcholine hyperkalemia 1982;61:83
    - release reduced by diphenylhydantoin (abstract) 1980;59:525
    - scavenging of potassium cardioplegic solution 1983;62:780
    - serum potassium levels during and after terbutaline 1981;60:723
    - succinylcholine increased plasma potassium 1975;54:680
    - succinylcholine-induced hyperkalemia in a patient with Parkinson's disease 1980;59:444
    - succinylcholine-induced increases in plasma catecholamine levels (letter) 1984;63:465
    - succinylcholine, repeated doses and renal failure 1975;54:746
  - sodium, effects on anesthetic requirement, compared with potassium and osmolality 1978;57:404
- **Isoflurane,** see Anesthetics, volatile
- **Iso-Indoklon,** see Anesthetics, volatile
- **Isoproterenol,** see
  - Heart
  - Sympathetic nervous system
  - Sympathomimetic agents
- **Isosorbide,** see
  - Anesthetic techniques, hypotensive
  - Pharmacology
- **Jehovah's Witnesses,** see Organizations
- **Journals,** see Anesthesiology, journals
- **Jugular vein,** see Veins
- **Kanamycin,** see Antibiotics
- **Kidney**
  - acute failure, pancuronium 1976;55:343
  - aortic valve replacement, anesthetic considerations 1975;54:24
  - blood flow 1983;62:499
    - changing following sodium nitroprusside during nephrolithotomy 1977;56:102
    - differences in autoregulation during anesthesia with halothane, methoxyflurane, or alphaprodine in dog 1978;57:389
    - during combination nitroprusside–dopamine infusions (abstract) 1980;59:530
    - effects of isoflurane and halothane anesthesia 1984;63:557
    - induction agents and renal hemodynamics 1982;61:853
    - methylene blue injection 1976;55:674
    - neurofibromatosis (case history) 1975;54:542
  - diuretics
    - cardiovascular and cation effects of urea 1981;60:641
    - effect of preoperative administration of furosemide (abstract) 1983;62:248
    - furosemide, recovery of evoked twitch response after pancuronium 1980;59:55
    - hyponatremia after administration in the presence of renal failure 1981;60:165
    - mannitol defect in oxygenation associated with 1979;58:145
    - mannitol, effects on blood volume and central hemodynamics during cerebral aneurysm surgery 1983;62:875
    - norepinephrine excretion, morphine anesthesia 1975;54:509
    - renal perfusion, nitroprusside and 1979;58:156
    - neurosurgery (abstract) 1982;61:213
  - function
    - effect of anesthetic dose of morphine 1975;54:357
    - enflurane, failure of, in altering renal responses to acute intracranial pressure increases 1978;57:200
    - methoxyflurane biotransformation, vaginal delivery or cesarean section 1976;55:415
    - nitroprusside, hypotension induced by effect on renal function 1978;57:521
    - nitrous oxide modification of halothane-altered 1977;56:690
    - renal function and stress response during halothane or fentanyl anesthesia 1981;60:552
  - mannitol, hyponatremia after administration in the presence of renal failure 1981;60:165
  - microsomes, extrahepatic biotransformation of halothane and enflurane 1981;60:129
  - nephrology
    - acute renal failure, prolonged neuromuscular blockade with pancuronium 1976;55:343
    - aortic valve replacement, anesthetic considerations 1975;54:24
    - effect of anesthetic doses of morphine on renal function 1975;54:357
    - renal effects, sevoflurane and methoxyflurane 1975;54:829
    - renal failure, succinylcholine effect on potassium 1975;54:746
    - renal transplantation, regional anesthesia 1976;55:69
    - severe hypertension, Wilms' tumor 1976;55:519
    - sevoflurane and methoxyflurane 1975;54:829
    - succinylcholine effect on potassium 1975;54:746
  - renal hypertension, neurofibromatosis (case history) 1975;54:542
  - transplantation (abstract) 1984;63:202
    - acute hemodynamic changes 1984;63:158
    - hyperkalemia in kidneys preserved with potassium 1980;59:283
    - regional anesthesia 1976;55:69
  - urea, cardiovascular and cation effects 1981;60:641
  - urinary retention, effect of epidural morphine and naloxone reversal

**Kidney**—*continued*
  - 1983;62:641
  - Wilm's tumor 1976;55:519

**Kyphoscoliosis,** see Complications

**Labetol,** see Sympathetic nervous system, alpha-adrenergic antagonist

**Laboratory screening**
  - unexpected hepatic dysfunction 1976;55:810

**Lactate,** see Metabolism

**Laparoscopy,** see
  - Surgery
  - Intubation, endotracheal
  - Intubation, tracheal

**Laryngoscopy,** see
  - Anesthetic techniques
  - Intubation, tracheal
  - Larynx
  - Surgery, laryngoscopy

**Laryngospasm,** see Larynx, spasm

**Laryngotracheoesophageal cleft,** see
  - Airway
  - Complications

**Larynx**
  - edema, postintubation croup in children 1977;56:501
  - intubation, complications 1984;63:335
  - laryngoscopy, and tracheal intubation, circulatory response to, with or without prior oropharyngeal lidocaine 1977;56:618
  - pneumatocele, a complication of percutaneous transtracheal ventilation (brief reports) 1976;55:600
  - postintubation complications, laryngeal pathology following long-term oral and nasal 1978;57:663
  - rediscovering the larynx (letter) 1983;62:855
  - spasm
    - as early indicator of aspiration 1978;57:119
    - extubation, controlled by lidocaine, in children 1978;57:506
  - stenosis, acromegaly 1976;55:57
  - trachea and, evaluation by xeroradiography (brief reports) 1976;55:598
  - translaryngeal intubation, acute respiratory failure 1976;55:195
  - transtracheal or translaryngeal (letter) 1983;62:371
  - use of kit as guide for endotracheal intubation 1977;56:287
  - vocal cord paralysis, following endotracheal intubation (questions and answers) 1977;56:321
  - see
  - Anesthesia, otolaryngologic
  - Surgery, otolaryngologic

**Lasers,** see
  - Equipment
  - Surgery, laryngoscopy

**Lavage,** see Lung

**Legal aspects of anesthesia,** see Medicolegal

**Leukocytes,** see Blood

**Liability,** see Medicolegal

**Lidocaine,** see
  - Anesthetics, local
  - Heart, arrhythmias

**Ligamentum flavum,** see
  - Anatomy
  - Anesthetic techniques, epidural

**Lincomycin,** see Antibiotics

**Lithium,** see Pharmacology

**Liver**
  - biliary spasm, narcotic-induced, reversed by glucagon 1980;59:946
  - biliary tract
    - effects of narcotics 1984;63:139
    - pressure changes induced by narcotic drugs and inhalation anesthetics 1979;58:120
    - pressure, narcotic-induced hypertension 1984;63:441
  - blood flow
    - during halothane anesthesia and hypoxia 1981;60:306
    - effects of isoflurane and halothane anesthesia 1984;63:557
    - hepatotoxicity and surgical trauma 1982;61:79
    - isoflurane, effect with or without 50% nitrous oxide 1983;62:499
    - phenobarbital-treated rats, halothane and hypoxia (abstract) 1980;59:558
    - relationship with halothane and hypoxia (letter) 1981;60:769
  - cirrhosis, portacaval shunt surgery (abstract) 1982;61:185
  - enzymes, inactivated by nitrous oxide 1982;61:75
  - function, during nitrous oxide anesthesia 1983;62:317
  - function, multiple laboratory screening 1976;55:810
  - function, protective effect of oxygen during halothane anesthesia 1978;57:481
  - halothane, injury 1982;61:824
  - halothane lesions 1975;54:332
  - hepatic clearance of lidocaine, during nitrous oxide anesthesia in dogs 1976;55:322
  - hepatics, enflurane (letter) 1980;59:890
  - hepatitis
    - cephalosporin (letter) 1980;59:806
    - diagnosis and management in operating-room personnel 1977;56:366
    - effects of isoflurane 1984;63:775
    - enflurane anesthesia 1980;59:146
    - fatal necrosis after halothane, with juvenile rheumatoid arthritis 1977;56:589
    - lesions 1975;54:332
    - pathology 1976;55:235
    - prevalence in anesthesia personnel 1984;63:433, 738
  - hypoxia
    - halothane-induced injury 1982;61:824
    - injury 1982;61:820
    - responses 1984;63:885
  - methionine synthetase
    - inactivated by nitrous oxide 1982;61:75
  - microsomes, extrahepatic
    - biotransformation of halothane and enflurane 1981;60:129
  - neuromuscular relaxants, pharmacokinetics and pharmacodynamics of gallamine in patients with total biliary obstruction 1981;60:289
  - pathology, in animals sensitized to a halothane metabolite and subsequent halothane exposures 1976;55:235
  - toxicity
    - and surgical trauma 1982;61:79
    - anesthetics 1982;61:812
    - anesthetic induced 1983;62:140, 146
    - anesthetic-induced injury 1984;63:1076
    - effect of halothane, isoflurane, and blood loss 1984;63:965
    - effects of isoflurane on halothane-induced hepatic injury 1984;63:888
    - halothane 1982;61:809
    - responses to volatile anesthetics: changes in surface scanning and enzyme leakage 1978;57:605
    - with celiac plexus block 1984;63:479
  - transplantation, (abstract) 1984;63:246

**Local anesthetics,** see Anesthetics, local

**Lofentanyl,** see
  - Analgesics
  - Anesthetics, intravenous

**Lorazepam,** see
  - Hypnotics, benzodiazepines
  - Premedication

**Lung**
  - absorption-excretion volume effect 1976;55:51
  - acute respiratory failure, goal-directed therapy 1980;59:831
  - airway pressure, effects of high-frequency jet ventilation 1984;63:1065
  - amine uptake, inhibition of 5-hydroxytryptamine removal by free radicals 1982;61:666
  - antibacterial defense mechanisms, effect of halothane 1979;58:505
  - aspiration
    - antacid (abstract) 1982;61:183
    - antacids 1982;61:288
    - antacids and gastric acid neutralization 1984;63:325
    - bronchial asthma pharmacology (editor's choice) 1975;54:227
    - bronchial blockade balloon-tipped catheter (brief reports) 1976;55:874
    - bronchial blockade, bronchopleural-cutaneous fistula in a child (brief reports) 1976;55:874
    - cimetidine for prophylaxis 1979;58:426

  combined effects of pH and volume (abstract) 1983;62:266
  foreign body in neonate 1977;56:726 (letter) 1984;63:1142
  pneumonia prophylaxis (editorial) 1983;62:1055
  pulmonary effects of volume and pH 1984;63:665
  pulmonary lesions after antacid and cimetidine (abstract) 1980;59:547
  tracheal, simple technique to minimize 1976;55:816
  unilateral hydrochloric acid (abstract) 1982;61:207
asthma
  halothane and enflurane protect against bronchospasm in dog 1978;57:629
  perioperative management 1984;63:844
atelectasis
  during anesthesia 1980;59:792
  inadvertent right main bronchial intubation 1983;62:851
bronchospasm 1981;60:839 1983;62:104
  cardiopulmonary bypass 1982;61:538
bronchus
  changes during prolonged cannulation 1980;59:759
  depression of mucociliary clearance by thiopental and halothane 1979;58:387
  effect of lidocaine in bronchoconstriction 1981;60:28
  halothane and ketamine failure to alleviate carcinoid syndrome 1980;59:621
  intrathoracic large airway circumference 1982;61:693
  mainstem rupture during general anesthesia 1979;58:59
  unusual airway problem (brief reports) 1976;55:746
capillary pressure, serum oncotic pressure 1982;61:496
compliance
  atropine and glycopyrrolate effects on lung mechanics 1981;60:85
  changes following chest physiotherapy 1980;59:207
edema 1984;63:363
  comparison of positive end-expiratory pressure and inspiratory positive pressure plateau in ventilation 1979;58:288
  during laparoscopy 1982;61:699
  effect of ketamine 1983;62:398
  following cardiopulmonary bypass 1978;57:367
  progesterone for Pickwickian syndrome, respiratory implications 1977;56:133
function
  airway response following topical anesthesia with lidocaine 1980;59:123
  atropine and glycopyrrolate effects on lung mechanics 1981;60:85
  before and after prolonged continuous positive airway pressure by mask (abstract) 1983;62:286
  gas exchange, pulmonary 1975;54:409
  influence on aging 1983;62:764
  noninvasive measurement of gas exchange 1980;59:263
  pancuronium, following pretreatment dose 1980;59:659
  postoperative recovery of 1981;60:46
hemodynamics, and baroreceptor reflexes during halothane and halothane-nitrous oxide anesthesia 1981;60:701
intramuscular succinylcholine in infants 1981;60:220
intravascular pressure (letter) 1984;63:89
intravascular pressures, capillary (letter) 1982;61:805
lavage, anesthetic management 1977;56:661
microsomes, extrahepatic biotransformation of halothane and enflurane 1981;60:129
obstructive pulmonary disease
  and respiratory complications during anesthesia 1983;62:975
  respiratory control 1980;59:865
oxygen toxicity, inhibition of 5-hydroxytryptamine removal by free radicals 1982;61:666
phagocytosis, general anesthesia 1975;54:501
physiotherapy, changes in lung/thorax compliance 1980;59:207
physiotherapy, effect on arterial oxygenation 1978;57:28
pneumocardiography, determinants and genesis of 1978;57:653
pneumonia, effects of positive end-expiratory pressure 1979;58:208
pneumothorax, suction applied to ventilator exhaust valve 1979;58:147
pulmonary vasculature, response to nitroprusside 1978;57:551
respiratory distress, model, high-frequency ventilation compared with conventional mechanical ventilation 1982;61:323
respiratory distress syndrome 1983;62:284
  (abstract) 1984;63:241
respiratory failure, management with combined high-frequency ventilation 1983;62:39
serotonin uptake, inhibition of 5-hydroxytryptamine removal by anesthetics 1982;61:671
shunting
  anesthetics and pulmonary venous admixture in pregnant and nonpregnant sheep 1979;58:318
  induced hypotension 1982;61:231
  one-lung anesthesia 1982;61:507
  perfusion characteristics during cardiopulmonary bypass and subsequent changes in alveolar-arterial oxygen tension gradients 1978;57:298
  serum, oncotic pressure 1982;61:496
  vasodilators and pulmonary venous admixture (abstract) 1980;59:532
trachea
  anesthesia for extensive resection of stenosis in infant 1979;58:431
  anesthetic management of patient with obstructing intratracheal mass 1977;56:295
  changes during prolonged cannulation 1980;59:759
  cilia, effect of halothane 1979;58:500
  effect of nitroglycerin on large airways 1983;62:421
  guinea pig muscle, comparison of procaine, lidocaine, and ketamine in inhibiting histamine-induced contracture in 1978;57:25
  larynx and, evaluation by xeroradiography (brief reports) 1976;55:598
  oxygen jet ventilation (letter) 1982;61:622
  oxygen jet ventilation during reconstruction of, in tracheal stenosis 1977;56:429
  pathology following intubation with endotracheal tube cuffs 1978;57:577
  sterile aspiration, nonhypoxemic system for 1977;56:449
tracheal cilia
  effect of halothane, enflurane and nitrous oxide 1980;59:426
  local anesthetics and ring activity 1978;57:448
tracheitis, airway management in children 1984;63:860
tracheal epithelium, squamous metaplasia, high volume, low pressure airway cuffs 1975;54:340
tracheal lidocaine
  circulatory changes, anesthetic induction 1976;55:77
  tracheal stenosis, resection 1976;55:191
tracheobronchial trauma, influence of suction catheter tip design 1976;55:290
tracheostomy, acute respiratory failure 1976;55:195
transplantation (abstract) 1984;63:251
vascular resistance, nitrous oxide 1980;59:323
vasculature, effects of dobutamine, dopamine, and isoproterenol (abstract) 1981;60:247
venous admixture, during high-frequency ventilation 1982;61:735
water (abstract) 1984;63:215, 216, 226

**Lymph**, see
  Blood
  Potency, anesthetic
**Machines, anesthesia**, see Equipment
**Magnesium**, see Ions
**Malignant pyrexia**, see Hyperthermia
**Malpractice**, see Medicolegal
**Mannitol**, see
  Fluid balance
  Kidney, diuretics
**Manpower** 1983;62:124
  changing medical specialties 1982;61:504
  migration of physicians to and from anesthesiology (letter) 1983;62:702
  nurse anesthetists
    auditing performance 1984;63:611
    drug abuse 1983;62:467
  recruitment, medical student views of anesthesiology 1979;58:443
  residents, national survey of medical student attitudes 1979;58:201
**Massage, cardiac**, see Heart, massage
**Maxillofacial surgery**, see Surgery
**Measurement techniques**
  airway obstruction, tests of, interrelationships and physiologic significance 1977;56:242
  anesthetic gases, response time of Narcotest monitor 1977;56:395
  anesthetics, halogenated, cross-sensitivity in the Engström EMMA 1984;63:75
  blood pressure
    (abstract) 1984;63:222
    effect of air bubbles (abstract) 1983;62:289
    infant blood pressure monitor 1981;60:742
    (letter) 1982;61:476
  calculators, hemodynamic monitoring with (letter) 1981;60:67
  cardiac output
    effect of catheter thrombus 1983;62:1031
    effect of halothane and pentobarbital on dispersion of indicator particles in central circulation 1977;56:68
    monitoring with pocket calculators (letter) 1981;60:67
    thermodilution computer (letter) 1982;61:162
    thermodilution injection (letter) 1982;61:544
  cardiovascular, hemodynamic tracking system 1980;59:169
  cerebral pH, changes during asphyxia, hypotension, and circulatory arrest 1977;56:817
  chromatography 1984;63:1059
  column 1984;63:1059
  cyanide, limitations for use in plasma and whole blood 1979;58:457
  dead space, mechanical ventilators 1980;59:488
  Doppler
    blood pressure monitoring 1979;58:526
    cardiac output (abstract) 1983;62:261
    headset adaptation for use with personalized earpiece (correspondence) 1977;56:469
    monitor, in cannulation of nonpalpable artery 1977;56:125
    percutaneous cannulation of weakly palpable arteries 1977;56:448
  radial artery cannulation 1984;63:346
  ultrasound, positioning the flow detector probe (letter) 1982;61:69
  echocardiography, ventricular diastolic volume and cardiac performance during halothane anesthesia 1979;58:23
  electrochemical detection 1984;63:1059
  electrodes, fentanyl–air–oxygen anesthesia in preterm infants 1981;60:331
  electromyogram
    evoked compound, instrument for continuous recording of 1977;56:260
    fade of neurally evoked compound, during neuromuscular block by *d*-tubocurarine 1977;56:271
  evoked potentials 1981;60:779
  fluoride assay, limitations 1982;61:786
  fluorinated metabolites, detection by sodium fusion 1980;59:61
  gas chromatography, elimination of metabolites after epidural anesthesia with 2-chloroprocaine 1983;62:1089
  gas tensions, transcutaneous $P\text{CO}_2$ 1981;60:504
  halothane, ultraviolet spectroscopy 1980;59:431
  high-performance liquid chromatography, determination of bupivacaine in plasma 1984;63:448
  liquid 1984;63:1059
  liquid-crystal thermometry, inaccuracy of 1982;61:284
  liquid-crystal thermometry 1978;57:669
  mass spectrometry, detecting anesthesia circuit dysfunction 1984;63:536
  motor blockade, assessment of motor blockade during epidural anesthesia 1983;62:839
  neuromuscular blockade
    100-hertz tetanus and train-of-four 1982;61:439
    cumulative dose-response curves for gallamine 1979;58:377
    monitoring 1980;59:308
    nondepolarizing, spontaneous recovery from 1977;56:55
    quantitative measurement of the isometric contraction of the adductor pollicis muscle 1983;62:602
    succinylcholine, during balanced anesthesia 1980;59:110
    tetanic fade and post-tetanic tension in absence of blocking agents 1978;57:102
  neuromuscular function, mechanical recovery after fazadinium 1982;61:225
  oximeter, evaluation of fiberoptic catheter 1982;61:676
  oxygen
    assessment of arterial oxygenation 1982;61:582
    fentanyl–air–oxygen anesthesia in preterm infants 1981;60:331
  pain, fentanyl anesthesia and painful tooth pulp sensations 1982;61:751
  pH, cerebral, changes during asphyxia, hypotension, and circulatory arrest in dog 1977;56:817
  pneumocardiography
    automated measurement and frequency analysis in 1978;57:647
    determinants and genesis of 1978;57:653
  pulmonary gas exchange, noninvasive, during general anesthesia 1980;59:263
  sensory block, tetanic electrical current 1980;59:796
  spectrometry, continuous measurement of uptake of anesthetic and respiratory gases (abstract) 1983;62:263
  temperature, liquid crystal thermometry 1979;58:351
  thermometric estimation of carbon dioxide output 1975;54:206
  tomography, cerebral computer, anesthetic considerations 1977;56:344
  transcutaneous
    (abstract) 1984;63:178
    monitoring during bronchoscopy and washout for cystic fibrosis 1983;62:357
    monitoring during one-lung anesthesia (abstract) 1983;62:288
    oxygen tension, trend indicator of arterial $P\text{O}_2$ 1982;61:252
    $P\text{CO}_2$ 1981;60:504
  transducers, pressure domes containing diaphragm, laboratory evaluation of 1978;57:67
  ultrasound, techniques for locating the internal jugular vein 1984;63:673
  venous, continuous monitoring in critically ill patients 1982;61:513
  venous oxygen saturation
    continuous postoperative measurement 1984;63:873
**Median nerve**, see Nerve
**Mediastinoscopy**, see Surgery, mediastinoscopy
**Medicolegal**
  acupuncture constitutes practice of medicine 1977;56:154
  anesthesiologist liable for patient's movement during eye surgery

    1977;56:320
  - anesthetic manufacturer not liable for death of patient (physician and the law) 1976;55:202
  - appendectomy settlement for brain damage (physician and the law) 1976;55:45
  - attorney urges study of doctor's professional relationships (physician and the law) 1976;55:756
  - cardiac arrest during surgery, brain damage (physician and the law) 1975;54:778
  - dentists settle for $250,000 in cardiac arrest case (physician and the law) 1975;54:398
  - informed consent suit against anesthesiologist (physician and the law) 1976;55:906
  - informed consent suit (physician and the law) 1976;55:906
  - instructions for witnesses (physician and the law) 1975;54:94
  - legal aspects of anesthesia, physician-patient relationship (questions and answers) 1976;55:463
  - liability
    - death of heart transplant donor (physician and the law) 1976;55:611
    - manufactured (physician and the law) 1976;55:202
    - no liability for death of patient during anesthesia (physician and the law) 1976;55:759
    - physician's, heart transplant donor (physician and the law) 1976;54:182
  - malpractice, attorney urges study of doctors professional relationship (editor's choice) 1976;55:756
  - missionary 1975;54:184
  - negligence
    - anesthesia death (physician and the law) 1975;54:679
    - not found in surgeon's failure to supervise anesthesiologist (physician and the law) 1976;55:459
  - physician-patient relationship, legal aspects (questions and answers) 1976;55:463
  - physician's travel expenses to seminar abroad may be nondeductible (physician and the law) 1975;54:464
  - $1,237,500 settlement for brain damage during appendectomy (physician and the law) 1976;55:45
  - $2,500,000 verdict for brain damage from cardiac arrest during surgery (physician and the law) 1975;54:778
  - $325,000 settlement for death from negligence in anesthesia (physician and the law) 1975;54:679

**Memory**
- absence of recall, general anesthesia 1976;55:696
- fentanyl effects 1980;59:948
- intraoperative
  - (abstract) 1984;63:185
  - during anesthesia 1983;62:239
  - following ketamine for open-heart surgery 1978;57:267
  - hypertensive crisis during high-dose fentanyl–diazepam–oxygen anesthesia 1983;62:698
- lorazepam, clinical evaluation 1976;55:522
- lorazepam premedication 1976;55:792
- perioperative awareness and recall 1976;55:513
- under regional anesthesia, intravenous lorazepam as a premedicant 1976;55:368

**Meningitis,** see Complications

**Meningoencephalocele,** see Complications

**Meperidine,** see Analgesics, narcotic

**Mepivacaine,** see Anesthetics, local

**Metabolism**
- acetate, failure to reverse myocardial depression in dogs anesthetized with halothane 1978;57:395
- adenosine triphosphate, antiarrhythmic action of, dogs 1982;61:423
- cortisol, extradural diamorphine and stress 1982;61:15
- definition (questions and answers) 1976;55:760
- diabetes
  - maternal and neonatal acid-base status and bupivacaine concentration in epidural anesthesia for cesarean section 1981;60:574
  - spinal anesthesia in diabetic parturients 1982;61:662
- fasting, anesthetics and liver toxicity, rats 1982;61:812
- glucose
  - effects of enflurane on release of insulin by pancreatic islets 1981;60:878
  - extradural diamorphine and stress 1982;61:15
  - maternal-fetal glucose homeostasis 1982;61:32
  - vulnerability of myelinated fibers to glucose lack 1984;63:15
- insulin, use of artificial beta cell during anesthesia 1980;59:950
- lactate, anesthesia and hemorrhage 1981;60:481
- malignant hyperthermia 1979;58:76
- myocardial, fentanyl effects during experimental ischemia 1980;59:644
- of sevoflurane and methoxyflurane, enzyme induced rats 1975;54:829

**Metabolism, drug,** see Biotransformation

**Methadone,** see Analgesics

**Methionine synthetase,** see Enzymes

**Methohexital,** see Anesthetics, intravenous

**Methoxyflurane,** see Anesthetics, volatile, methoxyflurane

**Methylene blue,** see Pharmacology

**Methylmethacrylate,** see Surgery, orthopedic

**Metoclopramide,** see
- Gastrointestinal tract, stomach
- Vomiting, antiemetics

**Metocurine,** see Neuromuscular relaxants

**Metoprolol,** see
- Heart
- Sympathetic nervous system, sympatholytic agents

**Microsomes,** see
- Biotransformation (drug)
- Liver
- Metabolism

**Microwave,** see Equipment

**Midazolam,** see
- Hypnotics, benzodiazepines
- Premedication

**Mitochondria,** see Metabolism

**Mitosis**
- nitrous oxide, effect on thymidine and methionine syntheses in pregnant rats 1983;62:738

**Monitoring**
- blood pressure, digital and sampled-data control during halothane anesthesia 1982;61:1010
- breathalyzer test and exposure to anesthetic gases (questions and answers) 1976;55:615
- carbon, detecting anesthesia circuit dysfunction 1984;63:536
- central venous and Swan-Ganz pressures (brief reports) 1975;54:549
- central venous pressure, comparison of internal and external jugular vein routes 1980;59:40
- central venous pressure (brief reports) 1975;54:157
- Doppler-assisted radial artery cannulation 1984;63:346
- EEG, computerized, prognostic use in surgery 1983;62:186
- EEG, activity and nitrous oxide 1981;60:283
- electrocardiography
  - comparison of CB$_5$ and V$_5$ leads 1981;60:849
  - esophageal lead 1982;61:781
  - for detecting myocardial ischemia 1984;63:343
- electromyogram, during succinylcholine infusion 1984;63:891
- esophageal, electrocardiography 1982;61:781
- evoked potentials
  - carotid endarterectomy 1982;61:879
  - effects of anesthetics on brainstem

**Monitoring**—*continued*
- evoked potentials—*continued*
  - auditory evoked potentials 1982;61:338
  - intraoperative hypoxia detected by 1981;60:437
  - somatosensory, neurosurgical operations (abstract) 1982;61:186
- gas monitor, Narkotest, calibration (brief reports) 1976;55:441
- infant blood pressure monitor 1981;60:742
- intraoperative spinal cord function, using hypnosis 1976;55:42
- jugular cannulation, ultrasound-simulated techniques 1984;63:673
- minimal respiration in man, using volumetric system 1975;54:232
- muscle twitch, during succinylcholine infusion 1984;63:891
- nerve, 100-hertz tetanus and train-of-four 1982;61:439
- nerve stimulator, neuromuscular blockade monitor 1980;59:308
- nerve stimulator for, in neuromuscular blockade 1978;57:13
- neuromuscular function
  - electrode/transducer system 1984;63:152
  - (letter) 1984;63:1139, 1141
- oxygen
  - assessment of arterial oxygenation 1982;61:582
  - evaluation of monitors 1981;60:53
  - evaluation of monitors (letter) 1981;60:539
  - (letter) 1984;63:962
- pulmonary arterial catheters, early diagnosis of myocardial ischemia 1981;60:789
- stimulator 1982;61:439
- succinylcholine infusion 1980;59:639
- temperature
  - inaccuracy of liquid crystal thermometry 1982;61:284
  - intraoperative 1983;62:211
- three-channel portable battery-powered (brief reports) 1975;54:546
- train-of-four stimulation, during succinylcholine infusion 1984;63:891
- vascular
  - blood pressure in great toe with simulated occlusion of dorsalis pedis artery 1978;57:453
  - hydromediastinum after arterial catheterization 1980;59:159
  - introducer for intraoperative percutaneous insertion of Swan-Ganz catheter 1977;56:444
  - percutaneous cannulation of weakly palpable arteries 1977;56:448
  - pulmonary artery catheters, pathophysiology of rupture of the pulmonary artery 1983;62:925
- vascular (letter) 1983;62:702
- venous oxygen, continuous postoperative measurement 1984;63:873

**Morphine,** see
- Analgesics
- Anesthetics, intravenous
- Premedication

**Multiple sclerosis,** see Complications

**Muscle, skeletal**
- blood flow, effect of chemical sympathectomy on 1977;56:653
- calcium uptake by isolated sarcoplasmic reticulum 1981;60:492
- electromyogram
  - evoked compound, instrument for continuous recording of 1977;56:260
  - fade of neurally evoked compound, during neuromuscular block by *d*-tubocurarine 1977;56:271
- local anesthetic toxicity
  - myotoxicity in rats and humans 1981;60:471
  - regeneration 1980;59:727
  - single and repeated injections of mepivacaine in rat 1980;59:275
- metabolism, halothane-induced defect, hyperthermia-susceptible pig 1980;59:250
- susceptibility to malignant hyperthermia 1983;62:324

**Muscular dystrophy,** see Complications

**Mutagenicity,** see Toxicity

**Myasthenia gravis,** see Complications

**Myocardium,** see Heart

**Myotonias,** see Complications

**Nalbuphine,** see
- Analgesics
- Antagonists, narcotic

**Naloxone,** see Antagonists, narcotic

**Naltrexone,** see Antagonists, narcotic

**Narcotics,** see Analgesics, narcotic

**Nausea,** see Vomiting

**Nebulization,** see
- Aerosols
- Equipment, humidifiers
- Humidification

**Needles,** see Equipment

**Neonate,** see
- Anesthesia, obstetric
- Anesthesia, pediatric

**Neostigmine,** see
- Antagonists, neuromuscular relaxants
- Enzymes, cholinesterase

**Nerve**
- cluneal
  - neuropathy (correspondence) 1978;57:381
  - pain following intragluteal injection 1978;57:138
- conduction
  - differential sensitivities of nerve fibers during pregnancy 1983;62:1070
  - margin of safety for transmission 1982;61:561
- damage, postoperative, back roll 1982;61:471
- differential blockade, lidocaine and bupivacaine 1983;62:754
- differential sensitivity
  - local anesthetics 1982;61:570
  - vulnerability of myelinated fibers to glucose lack 1984;63:15
- hypoosmotic solutions, neural responses to 1982;61:912
- median, compression following radial arterial puncture 1980;59:953
- spinal accessory, simple technique for block 1978;57:591
- steroid effects 1980;59:610
- stimulation
  - electroanesthesia 1976;55:536
  - transcutaneous, effect on postoperative pain 1983;62:1010
  - treatment of post-operative pain (abstract) 1980;59:541
- stimulator
  - analgesia from transcutaneous electrical stimulation 1981;60:81
  - comparison of insulated and uninsulated needles for locating peripheral nerves 1984;63:925
  - comparison of insulated vs uninsulated needles for electrical nerve location 1984;63:919
  - effect on dose–response curves for gallamine 1979;58:377
  - transcutaneous cranial electrical in reduction of narcotic requirements 1982;61:863
  - transcutaneous, narcotic requirements and (abstract) 1982;61:216
  - transcutaneous, postoperative pain management 1982;61:449
  - transcutaneous, treatment of reflex sympathetic dystrophy in a 6-year-old 1977;56:438
- transmission 1983;62:124

**Nerve block,** see Anesthetic techniques, regional

**Neurofibromatosis**
- renal hypertension, and cardiac dysrhythmias (case history) 1975;54:542

**Neuroleptanesthesia,** see
- Anesthetic techniques
- Anesthetics, intravenous

**Neuromuscular junction**
- antibiotics
  - block by polymyxin B 1977;56:373
  - comparison of lincomycin and clindamycin 1977;56:329
- electrode/transducer system 1984;63:152
- trimethaphan 1976;55:353

**Neuromuscular relaxants**
- action, pre- and postjunctional effects (letter) 1983;62:1137
- alcuronium

  effects on intraocular pressure 1983;62:521
  inotropic effects, canine heart muscle 1980;59:717
alcuronium (letter) 1984;63:543
allergy, life-threatening anaphylactoid reactions 1983;62:559
allergy (letter) 1984;63:88
atracurium
  (abstract) 1984;63:201, 223, 228, 283
  blocking drug 1982;61:721
  circulatory response 1976;55:485
  clinical pharmacology 1982;61:169
  clinical pharmacology (abstract) 1982;61:199, 723
  comparison with other currently available muscle relaxants 1983;62:524
  dosage, timing and correlation with degree of twitch suppression (abstract) 1983;62:246
  during halothane anesthesia 1983;62:207
  effects on lower esophageal pressure 1984;63:65
  hemodynamic effects in healthy patients (abstract) 1983;62:270
  in myasthenia gravis 1984;63:1127
  neuromuscular effects 1982;61:730
  pediatric pharmacology 1984;63:309
bretylium, effect on neuromuscular transmission 1982;61:442
dantrolene, cardiovascular and neuromuscular interactions 1984;63:473
decamethonium, as a substitute for succinylcholine (questions and answers) 1975;54:637
*d*-tubocurarine
  (abstract) 1984;63:211, 258
  antagonism of succinylcholine-induced contracture of denervated muscle by 1981;60:605
  burns and pharmacokinetics 1982;61:241
  burns trauma (abstract) 1980;50:549
  cardiovascular and neuromuscular effects in dogs 1980;59:26
  changes in blood pressure 1980;59:697
  comparative pharmacokinetics of (abstract) 1981;60:265
  comparison of non-depolarizing muscle relaxants in children 1981;60:862
  determinants of plasma protein binding 1983;62:870
  drug interactions 1980;59:678
  effect on breathing patterns 1983;62:809
  effect on neuromuscular transmission 1982;61:442
  fade of neurally evoked compound electromyogram during block by 1977;56:271
  in infants and children 1981;60:335
  inotropic effects, canine heart muscle 1980;59:717
  interaction with ketamine, in phrenic nerve-hemidiaphragm preparation in rat 1978;57:238
  interaction with pancuronium 1984;63:437
  interaction with tobramycin 1977;56:587
  lincomycin interaction 1975;54:103
  neonatal responses 1984;63:799
  neuromuscular blockade produced and maintained by 1981;60:175
  neuromuscular transmission and lithium 1982;61:399
  pancuronium-induced neuromuscular blockade, pyridostigmine 1975;54:317
  potentiation and prolongation of pancuronium blockade with (letter) 1981;60:229
  potentiation of neuromuscular blockade 1980;59:604
  protein binding effects 1983;62:160
  responses to, with changes in potassium 1978;57:417
  reversal of combination nondepolarized neuromuscular block 1983;62:1081
  sensitivity to, in steroid-treated myasthenia gravis 1978;57:132
  spontaneous recovery from nondepolarizing blockade, measurement of response 1977;56:55
  temperature and neuromuscular block 1981;60:18
  temperature and potency of (letter) 1981;60:455
fazadinium
  clinical pharmacokinetics of, in renal failure (abstract) 1980;59:529
  inotropic effects, canine heart muscle 1980;59:717
  mechanical recovery after 1982;61:225
gallamine 1980;59:484
  altered resting thumb tension and mode of stimulation 1979;58:377
  bolus and infusion administration 1982;61:847
  comparison with atropine as pretreatment 1977;56:493
  comparison with *d*-tubocurarine, effects on fasciculations after succinylcholine 1975;54:81
  (letter) 1981;60:912
  pharmacokinetics and pharmacodynamics in patients with total biliary obstruction 1981;60:289
hemodynamic effects, pancuronium and metocurine in combination 1981;60:12
interaction with antibiotics, neuromuscular effects 1979;58:107
interaction with local anesthetics, at neuromuscular junction 1978;57:580
interactions (abstract) 1980;59:533
malignant hyperthermia, variations in onset 1981;60:499
measurement of response
  nerve stimulator for 1978;57:13
  spontaneous recovery from nondepolarizing blockade 1977;56:55
  twitch depression and train-of-four ratio 1983;62:314
metocurine
  (abstract) 1984;63:214, 254
  and pancuronium in burned children (abstract) 1983;62:281
  burned patient 1982;61:614
  cardiovascular and neuromuscular effects in dogs 1980;59:26
  cardiovascular effects during enflurane anesthesia 1978;57:540
  comparison of non-depolarizing muscle relaxants in children 1981;60:862
  hemodynamic effects in patients with coronary artery disease receiving propranolol 1977;56:255
  inotropic effects, canine heart muscle 1980;59:717
  pancuronium and, advantages of combination 1981;60:12
  potency during halothane-$N_2O$ and $N_2O$-narcotic anesthesia 1978;57:116
  potentiation of neuromuscular blockade 1980;59:604
  protein binding effects 1983;62:160
  resistance, patients with residual hemiplegia 1980;59:624
nondepolarizing, neuromuscular blocking agents 1975;54:669
norcuron, pharmacokinetics of (abstract) 1982;61:176
Org NC 45
  antagonism by neostigmine, pyridostigmine, 4-aminopyridine 1980;59:31
  cardiovascular and neuromuscular effects in dogs 1980;59:26
pancuronium 1976;55:343, 1983;62:75
  100-hertz tetanus and train-of-four 1982;61:439
  (abstract) 1984;63:254, 258
  adult respiratory distress syndrome 1975;54:219
  adverse drug interaction 1982;61:473
  age, sex, and disease, effects on plasma binding 1983;62:29
  anaphylactoid reactions 1984;63:865
  antagonism by neostigmine in cats 1979;58:483
  antagonism of (abstract) 1982;61:178
  anticonvulsant medications and (abstract) 1982;61:203
  assessment of block with surface

- **Neuromuscular relaxants**—*continued*
  - pancuronium—*continued*
    - electrodes (abstract) 1981;60:244
    - binding sites, plasma or tissues (abstract) 1982;61:202
    - cardiovascular and neuromuscular effects in dogs 1980;59:26
    - cardiovascular effects during fentanyl anesthesia 1983;62:1059
    - cardiovascular effects of meperidine-$N_2O$ before and after 1977;56:669
    - combination with metocurine (abstract) 1983;62:251
    - comparison of non-depolarizing muscle relaxants in children 1981;60:862
    - dose requirement, neuromuscular block (abstract) 1980;59:549
    - *d*-tubocurarine induced neuromuscular blockade 1975;54:317
    - elimination 1982;61:313
    - esophageal pressure 1984;63:65
    - fasciculation, precurarization 1975;54:71
    - furosemide facilitates recovery of twitch response after 1980;59:55
    - gentamicin interaction, renal failure (letter) 1980;59:393
    - halothane 1979;58:497
    - in infants and children 1981;60:335
    - influence of succinylcholine on duration of blockade 1977;56:22
    - influence on circulatory response during thiamylal-$N_2O$ halothane anesthesia 1976;55:485
    - inotropic effects, canine heart muscle 1980;59:717
    - interaction with *d*-tubocurarine 1984;63:437
    - interaction with ketamine, in phrenic nerve-hemidiaphragm preparation of rat 1978;57:238
    - (letter) 1984;63:166
    - lithium, neuromuscular transmission 1982;61:399
    - malignant hyperthermia (letter) 1980;59:889
    - masseter spasm after 1980;59:509
    - metocurine and, advantages of combination 1981;60:12
    - metocurine combination (abstract) 1981;60:271
    - neostigmine and 4-aminopyridine antagonism of blockade with 1978;57:316
    - neostigmine and polymixin B, interaction and neuromuscular function 1976;55:224
    - neuromuscular and electrocardiographic responses 1983;62:50
    - nitroglycerin and 1980;59:117
    - pediatric cardiac anesthesia 1981;60:798
    - pharmacokinetics of (abstract) 1982;61:176
    - potassium efflux 1976;55:474
    - potentiation and prolongation with *d*-tubocurarine (letter) 1981;60:229
    - potentiation of neuromuscular blockade 1980;59:604
    - precurarization 1975;54:71
    - predetermination of dose requirement 1980;59:722
    - protein binding effects 1983;62:160
    - pulmonary function following pretreatment dose 1980;59:659
    - pyridostigmine, induced neuromuscular blockade 1975;54:317
    - recovery after laparoscopy 1984;63:51
    - resistance, patients with residual hemiplegia 1980;59:624
    - responses to, with changes in potassium 1978;57:417
    - reversal of combination nondepolarized neuromuscular block 1983;62:1081
    - severe hypertension with 1978;57:265
    - spontaneous recovery from nondepolarizing blockade, measurement of response 1977;56:55
    - state of general anesthesia and (editorial) 1979;58:449
    - temperature and neuromuscular block 1981;60:18
    - temperature and potency of (letter) 1981;60:455
  - pretreatment
    - adverse effects of increased succinylcholine 1975;54:282
    - circulatory changes during anesthetic induction 1976;55:77
  - reversal, glycopyrrolate and atropine, difference 1980;59:431
  - succinylcholine 1983;62:75
    - (abstract) 1984;63:206, 240
    - allergy to (letter) 1981;60:456
    - anaphylaxis, penicillin allergy 1980;59:944
    - antagonism of contracture of denervated muscles by *d*-tubocurarine 1981;60:605
    - apnea, prolonged (case history) 1976;55:737
    - asystole after single dose of 1978;57:135
    - bradycardia 1975;54:705
    - changes in serum potassium in patients with infections 1983;62:327
    - characteristics of neuromuscular blockade with, in neonates 1978;57:63
    - characteristics of phase II block (abstract) 1981;60:255
    - characteristics of succinylcholine-produced phase II neuromuscular block during enflurane, halothane, and fentanyl anesthesia 1981;60:192
    - clinical characteristics of, during balanced anesthesia 1980;59:110
    - comparison of gallamine and atropine as pretreatment before 1977;56:493
    - congenital pyruvate kinase deficiency 1982;61:620
    - contraindication 1979;58:61
    - correlation of plasma cholinesterase and duration of, in pregnancy 1977;56:78
    - decamethonium (questions and answers) 1975;54:637
    - diazepam pretreatment 1980;59:932
    - dose relationships of tachyphylaxis and phase II block (abstract) 1980;59:535
    - *d*-tubocurarine increased 1975;54:282
    - effect on plasma catecholamine levels 1983;62:627
    - effect on potassium concentrations 1984;63:1146
    - effects on intracranial pressure (letter) 1984;63:620
    - fasciculation, comparison of gallamine with *d*-tubocurarine 1975;54:81
    - hyperkalemia in a patient with Parkinson's disease 1980;59:444
    - in infants and children 1981;60:335
    - in obstetrics (letter) 1983;62:1051
    - increased plasma catecholamine levels (letter) 1984;63:465
    - increased sensitivity to, and cholinesterase 1978;57:422
    - indicator of atypical pseudocholinesterase 1984;63:869
    - influence on duration of pancuronium blockade 1977;56:22
    - interaction with ketamine, in phrenic nerve-hemidiaphragm preparation of rat 1978;57:238
    - intracranial and hemodynamic changes 1983;62:1006
    - intracranial pressure in neurosurgical patients (abstract) 1980;59:550
    - muscle electromechanical correlations 1984;63:891
    - muscle pain, effects of diazepam 1979;58:314
    - muscle pains induced by, and diazepam 1978;57:295
    - myoglobinuria, halothane 1976;54:680
    - neuromuscular block reexamined (letters) 1980;59:633, 634
    - newborn hypoventilation 1975;54:38
    - pancuronium, potassium efflux 1976;55:474
    - plasma cholinesterase activity and tachyphylaxis 1982;61:941
    - plasma potassium, increased 1975;54:680
    - postoperative sore throat (abstract) 1983;62:253
    - preoperative glycopyrrolate and atropine 1980;59:686

    - pretreatment for prevention of succinylcholine-induced myalgia 1983;62:59
    - prevention of hyperkalemia (abstract) 1981;60:245
    - prolonged neuromuscular blockade in parturient 1983;62:444
    - pulmonary edema in infants 1981;60:220
    - radiation and hyperkalemia 1982;61:83
    - release of catecholamines (abstract) 1982;61:203
    - renal failure, serum potassium 1975;54:746
    - requirements during halothane–nitrous oxide anesthesia (abstract) 1983;62:251
    - resistance 1979;58:57
    - responses to, with changes in potassium 1978;57:417
    - side effects (questions and answers) 1975;54:637
    - spontaneous recovery from nondepolarizing blockade, measurement of response 1977;56:55
    - tachyphylaxis and phase II block development 1980;59:639
    - thiamylal
      - tracheal intubation and, circulatory changes in patients with coronary artery disease 1976;55:232
      - with *d*-tubocurarine pretreatment, anesthetic induction 1976;55:77
    - thiopental and, intraocular pressure 1975;54:471
    - train-of-four fade, and edrophonium antagonism of neuromuscular block 1976;55:663
  - vecuronium
    - (abstract) 1984;63:177, 218
    - and succinylcholine for cesarean section 1983;62:909
    - cardiovascular effects during fentanyl anesthesia 1983;62:1059
    - comparison with other currently available muscle relaxants 1983;62:524
    - effect of hypocarbia on anesthetic recovery 1984;63:608
    - elimination of 1982;61:313
    - recovery after laparoscopy 1984;63:51
    - safety and efficacy in pediatric anesthesia 1983;62:1083
    - verapamil-induced blockade reversal 1984;63:155
  - verapamil, neuromuscular and electrocardiographic responses 1983;62:50
- **Neuromuscular transmission**
  - lithium 1982;61:399
  - measurement
    - electrode type and placement (abstract) 1980;59:560
    - recovery from non-depolarizing neuromuscular blockade (abstract) 1980;59:524
  - nerve stimulator, cumulative dose-response curves for gallamine 1979;58:377
  - nucleotides 1981;60:91
  - prejunctional and postjunctional cholinoceptors 1980;59:935
  - stimulator, nerve, monitoring 1980;59:308
  - tetanic stimulation, in absence of neuromuscular blocking agents 1978;57:102
  - train-of-four, effect of neuromuscular relaxant antagonists 1983;62:314
  - verapamil, effects on indirect muscle twitch responses 1983;62:827
- **Neuropathy,** see
  - Complications
  - Nerve
- **Neurosurgery,** see Surgery, neurologic
- **Neurosurgical anesthesia,** see Anesthesia, neurosurgical
- **Nifedipine,** see
  - Heart
  - Pharmacology
- **Nitrogen dioxide,** see Anesthetics, gases, trace concentrations
- **Nitroglycerin,** see
  - Anesthetic techniques, hypotensive
  - Pharmacology
  - Surgery, cardiac
- **Nitroprusside,** see
  - Anesthetic techniques, hypotensive
  - Pharmacology
- **Nitrous oxide,** see Anesthetics, gases
- **Norcuron,** see Neuromuscular relaxants
- **Norepinephrine,** see Sympathetic nervous system
- **Obesity,** see Complications, obesity
- **Obstetric anesthesia,** see Anesthesia, obstetric
- **Obstruction,** see
  - Airway
  - Arteries
  - Gastrointestinal tract
  - Lung
- **Operating rooms**
  - air pollution, nitrous oxide exposure 1978;57:216
  - communication system 1983;62:454
  - exhaust systems
    - anesthetic pollution control, mechanical aspects 1977;56:769
    - monitoring occupational exposure to inhalation anesthetics 1977;56:778
  - fire, potential ignition source 1976;55:217
  - fires (case history) 1975;54:152
  - humidity (quesitons and answers) 1976;55:134
  - personnel 1979;58:302
  - personnel, effect of anesthetic wastes (questions and answers) 1976;55:760
  - pollution, government perspectives and guidelines 1977;56:775
  - temperature, effect on patient body temperature 1980;59:852
- **Ophthalmology,** see
  - Eye
  - Surgery ophthalmologic
- **Opioids,** see Analgesics
- **Oral surgery,** see Surgery, dental, maxillofacial
- **Organizations**
  - Anesthesia Foundation 1980;59:232
    - book award 1978;57:159
  - Jehovah's Witnesses, method of blood conservation in 1978;57:279
  - World Federation of Societies of Anesthesiologists 1980;59:87
- **Orthopedics,** see Surgery, orthopedic
- **Osmolality,** see
  - Blood
  - Cerebrospinal fluid
  - Kidney, urine
- **Otolaryngology,** see Surgery, laryngoscopy
- **Ouabain,** see Heart
- **Oximeter,** see Measurement techniques, oxygen
- **Oxygen**
  - air blending
    - oxygen–air, nomogram 1977;56:290
    - alveolar-arterial oxygen tension difference 1975;54:433
    - factors affecting, open heart surgery 1976;55:315
  - alveolar-arterial tension gradients, perfusion characteristics during cardiopulmonary bypass 1978;57:298
  - alveolar oxygen tension, calculation (correspondence) 1978;57:746
  - anesthetic effect 1976;55:734
  - arterial
    - hypoxemia, intravenous ketamine 1976;55:311
    - oxygenation, decreased, sodium nitroprusside (brief reports) 1976;55:880
    - oxygenation during intubation 1981;60:313
    - oxygenation during laryngoscopy intubation 1981;60:316
    - oxygenation, effects of intraoperative PEEP 1975;54:427
  - arteriovenous oxygen content, difference in shunt calculation 1975;54:198
  - chest physiotherapy, effect on $PaO_2$ 1978;57:28
  - consumption
    - continuous $\dot{V}O_2$ and $\dot{V}CO_2$ measurements during endotracheal anesthesia 1982;61:362
    - correlation with cardiovascular dynamics during $N_2O$–fentanyl and $N_2O$–thiopental anesthesia in dog 1978;57:37

- **Oxygen**—*continued*
  - consumption—*continued*
    - effect of $Pa_{CO_2}$ during cardiopulmonary bypass 1976;55:269
    - heart, clinical anesthesia 1980;59:229
  - gradients, fluctuating hypoxemia and pulmonary shunting following fatal head trauma 1977;56:129
  - gradients, A-a$D_{O_2}$ after open heart surgery 1976;55:315
  - hyperbaric, hepatoprotective effect during halothane anesthesia 1978;57:481
  - measurement, fiberoptic catheter oximeter 1982;61:676
  - mixed venous, continuous monitoring in critically ill patients 1982;61:513
  - monitoring
    - (abstract) 1984;63:178
    - assessment of arterial oxygenation 1982;61:582
    - evaluation of monitors 1981;60:53
    - evaluation of monitors (letter) 1981;60:539
  - oxyhemoglobin dissociation, cardiac disease and anesthesia 1980;59:751
  - purity
    - USP medical 1979;58:441
    - USP standards (letters) 1980;59:314
  - tension
    - compressed air–$O_2$-anesthetic mixtures for neonate 1977;56:127
    - critical level in anesthesia (abstract) 1982;61:196
    - general anesthesia 1982;61:950
    - oxygenation during intubation 1981;60:313
    - oxygenation during laryngoscopy intubation 1981;60:316
    - transcutaneous, as trend indicator of arterial $P_{O_2}$ 1982;61:252
  - tension difference, postoperative alveolar-arterial 1975;54:433
  - therapy, in athletes and firemen 1977;56:155
  - tissue, clinical medicine 1982;61:527
  - toxicity
    - case history 1976;55:588
    - inhibition of 5-hydroxytryptamine removal by free radicals 1982;61:666
    - intermittent exposure to 40 percent prolongs rat survival in 100 percent 1977;56:847
  - transport, patterns with cardiac surgery (abstract) 1983;62:281
  - uptake
    - diffusion in hyperoxia following preoxygenation 1977;56:59
    - noninvasive measurement 1980;59:263
  - viscosity, gas effects in anesthesia 1980;59:192
- **Oxyhemoglobin,** see Oxygen
- **Oxytocic drugs,** see Anesthesia, obstetric
- **Pacemakers,** see
  - Equipment
  - Heart
  - Ventilation, artificial
- **Pain**
  - acupuncture in obstetrics 1975;54:83
  - bladder, treatment with transsacral nerve block 1982;61:46
  - causalgia, phantom tongue 1979;58:436
  - central nervous system, serotonin 1981;60:354
  - chronic
    - analgesic effect of transcutaneous electrical stimulation 1981;60:81
    - in depression 1984;63:1025
    - with somatization disorder 1984;63:163
  - experimental
    - cognitive reversal of expected nitrous oxide analgesia 1983;62:1073
    - effect of intranasal cocaine in man 1982;61:358
  - hypophysectomy, alcohol-induced pituitary adenolysis 1979;58:279
  - intractable, in adiposis dolorosa 1976;55:257
  - intractable, use of intrathecal cold saline (questions and answers) 1976;55:131
  - measurement, fentanyl anesthesia and painful tooth pulp sensations 1982;61:751
  - mechanism
    - dual-system hypothesis (letter) 1982;61:886
    - effect of general anesthetics in primates (abstract) 1983;62:279
  - myofascial, local anesthetics in stimulus analgesia 1981;60:752
  - needle insertion (letter) 1984;63:373
  - pathologic
    - abdominal, alcohol celiac plexus nerve block 1977;56:01
    - alcohol-induced adenolysis of pituitary: control of intractable cancer pain 1977;56:414
    - treatment of chronic 1977;56:118
  - peripheral nervous system, vulnerability of myelinated fibers to glucose lack 1984;63:15
  - phantom limb, care of patients in pain clinic 1977;56:842
  - postoperative
    - attitudes toward postoperative analgesic care 1983;62:70
    - brachial plexus block for relief after mastectomy 1982;61:986
    - bupivacaine–morphine epidural anesthesia for prostatectomy 1981;60:818
    - comparison of dezocine and meperidine as postoperative analgesics 1978;57:563
    - comparison of intramuscular and epidural morphine in the grossly obese 1984;63:583
  - continuous epidural infusion of morphine 1984;63:757
  - effect of hydroxyzine on morphine analgesia 1980;59:690
  - effect of transcutaneous nerve stimulation 1983;62:1010
  - effects of epidural buprenorphine 1984;63:593
  - effects of extradural morphine and heroin 1984;63:629
  - epidural morphine for pain after cesarean delivery 1983;62:666
  - epidural morphine for relief of 1982;61:93, 236
  - influence of epidural fentanyl 1983;62:727
  - (letter) 1984;63:372
    - local anesthetics in man 1982;61:418
    - management by fenoprofen and morphine 1982;61:1002
    - morbid obesity 1980;59:902
    - narcotics for analgesia 1980;59:473
    - pulmonary function and (abstract) 1982;61:171
  - relief following acupuncture 1976;55:229
  - sciatica
    - delayed onset of epidural anesthesia 1981;60:874
    - subarachnoid corticosteroid injection 1978;57:313
  - serotonin, central nervous system 1981;60:854
  - spinal cord stimulation, facilitation of primary afferent depolarization 1982;61:410
  - tourniquet, transcutaneous electrical stimulation 1981;60:720
  - transcutaneous electrical nerve stimulation, failure to alleviate pain 1981;60:720
  - transcutaneous electrical stimulation, increased skin temperature during 1980;59:22
  - trigger points, surgical scars 1982;61:518
- **Palsy,** see Complications, neurologic
- **Pancuronium,** see Neuromuscular relaxants
- **Paracervical block,** see Anesthetic techniques, regional
- **Paraplegia,** see Complications, paralysis
- **Parasympathetic nervous system**
  - atropine
    - alone and with morphine and scopolamine as intravenous surgical premedicants 1977;56:606
    - cardiovascular effects of, in vagotomized dogs under halothane anesthesia 1977;56:338
    - comparison with gallamine as pretreatment 1977;56:493
    - domperidone effects, esophagus 1980;59:921
    - effect on gastric secretions in obesity 1981;60:37

    effects on lung mechanics 1981;60:85
    fetal and maternal cardiovascular effects 1983;62:426
    glycopyrrolate and, postanesthetic arousal times 1980;59:431
    glycopyrrolate and, preoperative, effect on arrhythmias and succinylcholine 1980;59:686
    hemodynamic effects and placental transfer in the pregnant ewe 1981;60:710
    intravenous, effect on heart rate and arterial pressure 1975;54:262
    parasympathetic blockade and neostigmine 1981;60:557
    pre- and post-anesthetic use in patients with glaucoma (questions and answers) 1976;55:460
    pupil size, muscle relaxant reversal 1980;59:615
    racial mydriatic response to premedication with 1978;57:572
    transient blindness following intravenous administration 1977;56:872
  glycopyrrolate
    and antacids (correspondence) 1978;57:145
    as premedication, control of gastric acidity by, in parturient 1977;56:642
    atropine and, postanesthetic arousal times 1980;59:431
    atropine and, preoperative, effect on arrhythmias and succinylcholine 1980;59:686
    comparison with atropine during reversal of nondepolarizing neuromuscular block with neostigmine 1977;56:182
    effect on gastric secretions in obesity 1981;60:37
    effects on lung mechanics 1981;60:85
    fetal and maternal cardiovascular effects 1983;62:426
    hemodynamic effects and placental transfer in the pregnant ewe 1981;60:710
    parasympathetic blockade and neostigmine 1981;60:557
  scopolamine
    alone and with morphine and atropine as intravenous surgical premedicants 1977;56:606
    racial mydriatic response to premedication with 1978;57:572
    reduction of enflurane-induced spike activity 1980;59:417
**Paravertebral blocks,** see
  Anesthetic techniques, regional, sympathetic
  Anesthetic techniques, regional, paravertebral
**Parkinsonism,** see Complications
**Partition coefficients,** see Solubility
**Patch, epidural,** see
  Anesthetic techniques, epidural
  Complications, headache, spinal
**Pediatric anesthesia,** see Anesthesia, pediatric
**PEEP,** see Ventilation, positive end-expiratory pressure
**Penicillin,** see Antibiotics
**Penis,** see
  Anesthetic techniques, regional
  Complications, priapism, ejaculation
**Pentazepam,** see Analgesics
**Pentazocine,** see Analgesics
**Pentobarbital,** see
  Anesthetics, intravenous
  Hypnotics, barbiturates
**Perfluorochemicals,** see
  Blood
  Pharmacology
**Pericardium,** see Heart
**Peridural,** see Anesthetic techniques, epidural
**Pethidine,** see Meperidine
**pH,** see
  Acid-base equilibrium, pH
  Carbon dioxide
**Phantom limb,** see Pain
**Phantom sensation,** see Pain
**Pharmacodynamics**
  *d*-tubocurarine, neonatal responses 1984;63:799
**Pharmacokinetics**
  aging and fentanyl 1982;61:968
  alfentanil 1982;61:657
  aminophylline
    and uptake 1983;62:733
    cardiorespiratory effects and, during halothane anesthesia 1980;59:186
  diazepam
    effects of age and sex on bioavailability 1983;62:01
    in patients with severe burns 1983;62:293
  *d*-tubocurarine
    in patients with thermal injury 1982;61:241
    neonatal responses 1984;63:799
  eating, increase in anesthetic uptake, excretion, and blood solubility after, in man 1978;57:224
  etidocaine, effects in fetal and neonatal lambs and adult sheep 1982;61:104
  etomidate, infusion regimen for hypnosis 1983;62:654
  fentanyl
    aortocoronary bypass surgery 1982;61:972
    during pediatric cardiac surgery 1984;63:577
    effects on EEG 1984;63:489
    ventilatory depression during and after anesthesia 1983;62:966
  gallamine, bolus and infusion administration 1982;61:847
  halothane
    effect of spontaneous versus controlled ventilation on alveolar concentration in dogs 1977;56:32
    error in sampling of exhaled gases (letter) 1983;62:955
    uptake and distribution in infants 1983;62:404
  pharmacokinetics, inhalation anesthetics 1982;61:587
  inhalation anesthetics, comparison by three-compartment linear model 1982;61:587
  intravenous, epinephrine and spinal anesthesia 1982;61:746
  intravenous drugs, review 1978;57:704
  intravenous procaine, infusion in humans 1979;58:382
  ketamine, plasma levels in surgical patients 1982;61:87
  local anesthetics, during plexus blocks 1977;56:852
  meperidine, gastric levels in surgical patients 1979;58:88
  scientific basis for drug selection 1978;57:603
  spinal anesthesia
    effects of epinephrine on lidocaine (letter) 1984;63:542
    effects of phenylephrine and neural blockade after lidocaine 1984;63:129
    uptake and elimination of local anesthetics 1983;62:1013
  subarachnoid, epinephrine and spinal anesthesia 1982;61:746
  uptake and excretion of 1-bromo-1,2,2-triflurocyclobutane, in man 1976;55:853
**Pharmacology**
  adenosine, hypotensive effects 1982;61:273
  adenosine triphosphate, hypotensive effects 1982;61:273
  aminophylline 1983;62:115
    adverse drug interaction with pancuronium 1982;61:473
    antagonizes diazepam 1984;63:900
    cardiac arrhythmias in experimental animals 1981;60:517
    cardiorespiratory effects and, during halothane anesthesia 1980;59:186
    cardiovascular effects with ketamine 1982;61:685
    diazepam antagonist 1981;60:767
    effect on arrhythmogenicity of isoflurane 1983;62:568
    halothane anesthesia, experimental animals 1980;59:410
    interaction with halothane, multiform ventricular tachycardia due to 1978;57:740
    (letter) 1982;61:307
    review of 1981;60:587

**Pharmacology**—*continued*
- aminophylline—*continued*
  - safety of enflurane following administration of 1981;60:871
  - theophylline drug incompatibilities (letter) 1982;61:547
  - uptake and pharmacokinetics 1983;62:733
- chloralose, effects of anesthetics on brainstem auditory evoked potentials 1982;61:338
- cimetidine
  - and congenital tracheoesophageal fistula (letter) 1983;62:620
  - effect on gastric fluid volume and pH 1979;58:183
  - effect on morphine-induced ventilatory depression (abstract) 1983;62:270
  - effects on gastric contents 1984;63:903
  - efficacy and safety (abstract) 1981;60:244
  - oral antacid in obstetric anesthesia (abstract) 1981;60:246
  - preanesthetic effect on gastric fluid pH and volume 1984;63:40
- cryptenamine, control of reflex response to sodium nitroprusside 1980;59:909
- dantrolene, cardiovascular and neuromuscular interactions 1984;63:473
- diethylstilbestrol, therapy, plasma pseudocholinesterase deficiency and 1978;57:726
- diuretics, furosemide facilitates recovery of evoked twitch response after pancuronium 1980;59:55
- dopamine, reduction of hypoxic ventilatory drive 1982;61:333
- general, pressures and people 1978;57:06
- glycopyrrolate, preanesthetic effect on gastric fluid pH and volume 1984;63:40
- ketanserin, treatment of postoperative hypertension after CABS 1983;62:63
- lithium
  - and neuromuscular transmission 1982;61:399
  - paroxysmal left bundle branch block during nitrous oxide anesthesia in patient on 1977;56:868
  - role in clinical anesthesiology (questions and answers) 1977;56:462
- methylene blue, hypertension and decreased renal blood flow 1976;55:674
- metoclopramide, effects on gastric contents 1984;63:903
- nifedipine
  - effect on the circulation during morphine–$N_2O$ and halothane anesthesia (abstract) 1983;62:284
  - intracranial pressure (abstract) 1983;62:254
  - intracranial pressure during hypotension 1983;62:1078
  - preoperative management (letter) 1983;62:1138
- nitroglycerin
  - absorption to polyvinylchloride 1982;61:541
  - (abstract) 1984;63:203, 263
  - coronary artery surgery (abstract) 1982;61:177
  - for pulmonary congestion in patients with mitral valve disease 1979;58:143
  - hemodynamic effects of 1982;61:927
  - methemoglobinemia associated with organic nitrate therapy 1979;58:521
  - neuromuscular blockade produced by gallamine, succinylcholine, *d*-tubocurarine, pancuronium and 1980;59:117
  - vasodilation with (letter) 1982;61:887
- nitroprusside
  - (abstract) 1984;63:190
  - hemodynamic and hormonal changes and prevention with intravenous propranolol (abstract) 1983;62:259
  - limitations of cyanide electrodes 1979;58:457
  - propranolol premedication and hypotension 1984;63:125
  - reaction to toxicity (abstract) 1983;62:247
  - regional blood flow (abstract) 1983;62:262
  - vasodilation with (letter) 1982;61:887
- perfluorocarbons, liquid–gas partition coefficients of halothane and isoflurane 1984;63:690
- phenytoin
  - in cerebral ischemia 1979;58:165
  - influence on hypoxic survival in combination with hypothermia or hyperthermia 1981;60:867
  - reduction of anoxic cerebral potassium 1981;60:41
  - treatment of cerebral ischemia (letter) 1981;60:616
- preservatives, subarachnoid neurotoxicity of acetone sodium bisulfite (abstract) 1983;62:289
- ranitidine
  - effects on gastric contents 1984;63:903
  - prophylaxis against Mendelson's syndrome 1982;61:130
- ritodrine
  - pulmonary edema following (letter) 1981;60:695
  - serum potassium levels during (abstract) 1982;61:191
- severe bronchial asthma (editor's choice) 1975;54:227
- sodium bisulfite, induced chronic neurological deficits 1984;63:445
- sodium nitroprusside
  - hypotensive effects of 1982;61:273
  - reflex responses to 1980;59:909
- tachyphylaxis, cholinesterase and succinylcholine 1982;61:941
- terbutaline
  - hypokalemia in obstetrical patients 1980;59:917
  - pregnant patients 1980;59:391
  - pulmonary edema during (letter) 1981;60:695
  - serum potassium levels 1981;60:723
- tetrodotoxin, effects on intracranial pressure 1984;63:1005
- theophylline 1983;62:115
  - antagonism of neuromuscular blockage by 1979;58:139
  - arrhythmogenicity in combination with halothane (letters) 1979;58:259
- verapamil
  - (abstract) 1984;63:268, 269, 272
  - and neuromuscular transmission (letter) 1983;62:1048
  - cardiovascular and neuromuscular interactions 1984;63:473
  - clinical and neuromuscular effects in pediatric patients (abstract) 1983;62:264
  - during coronary artery bypass graft surgery 1983;62:821
  - effect on MAC for halothane (abstract) 1983;62:274
  - effect on vecuronium neuromuscular blockade 1984;63:155
  - effects on indirect muscle twitch responses 1983;62:827
  - for treatment of arrhythmias after cardiopulmonary bypass 1984;63:460
  - hemodynamic effects and placental transfer (abstract) 1983;62:277
  - hemodynamic interactions with halothane 1984;63:791
  - neuromuscular and electrocardiographic responses 1983;62:50
- veratrum alkaloids, control of reflex response to sodium nitroprusside 1980;59:909

**Phenobarbital,** see
- Anticonvulsants
- Biotransformation (drug)
- Hypnotics, barbiturates
- Induction, enzyme

**Phenol,** see Anesthetics, local

**Phenylalanine,** see Proteins, amino acids

**Phenytoin,** see Pharmacology

**Pheochromocytoma,** see Surgery, pheochromocytoma

**Phosphorylase,** see Enzymes

**Physical status,** see Risk

**Physics**
- dissociation constants, temperature dependence of local anesthetics 1983;62:1025
- specific gravity
  - isobaric tetracaine spinal anesthesia and lithotomy position 1981;60:810

    - normal cerebrospinal fluid and tetracaine density 1981;60:814
- vapor pressures, volatile anesthetics 1979;58:322
- viscosity, gas effects in anesthesia 1980;59:192

**Physiotherapy**, see Lung, chest

**Physostigmine**, see Antagonists, miscellaneous

**Pickwickian syndrome**, see Complications, obesity

**Pituitary**, see
- Brain
- Surgery, neurologic

**Placenta**
- (abstract) 1984;63:176
- atropine and glycopyrrolate in the pregnant ewe 1981;60:710

**Plasma**, see Blood

**Plastic surgery**, see Surgery, plastic

**Platelets**, see Blood

**Pneumatocele**, see Complications

**Pneumocardiography**, see
- Heart
- Lung
- Measurement techniques

**Pneumocephalus**, see Complications

**Pneumonia**, see
- Complications
- Lung

**Pneumoperitoneum**, see Complications

**Pneumothorax**, see Lung

**Pollution**, see
- Anesthetics, gases, trace concentrations
- Anesthetics, volatile, trace concentrations
- Equipment, exhaust systems

**Polymyxin B**, see Antibiotics

**Polypeptides**
- β-endorphin, clearance from cerebrospinal fluid 1984;63:511
- brain, anesthesia effects (abstract) 1982;61:223
- endorphins, plasma and cerebrospinal fluid levels, pregnancy and parturition 1982;61:893
- renin–angiotensin, effects on blood pressure 1984;63:482
- renin–angiotension 1981;60:569

**Position**
- central venous catheters, tip migration 1984;63:949
- effects
    - anesthesia related to (questions and answers) 1977;56:325
    - cardiovascular, response to anesthesia in the seated position 1983;62:648
    - displacement of right atrial and endotracheal catheters with neck flexion 1978;57:371
    - seated (abstract) 1982;61:201
    - sitting, right atrial catheterization (abstract) 1982;61:205
- lateral sitting, neurosurgery 1976;55:326
- semirecumbent versus supine, effect on postoperative oxygenation in markedly obese subjects 1976;55:37
- spread of epidural anesthesia 1981;60:584
- Trendelenburg (abstract) 1984;63:239

**Positive end-expiratory pressure**, see Ventilation

**Potassium**, see Ions

**Potency, anesthetic**
- age, cyclopropane used to test anesthetic requirement in the elderly 1984;63:998
- age factors, age-dependent responses to halothane 1981;60:182
- barbiturates and nitrous oxide susceptibility 1984;63:35
- clonidine reduction of halothane MAC 1982;61:741
- convulsant gases and anesthetics 1981;60:464
- ED$_{50}$
    - measurement of anesthetic potency 1981;60:380
    - potencies of nitrous oxide in mice bred for resistance or susceptibility 1981;60:646
- fentanyl, comparison with thiopental 1983;62:151
- fetal MAC, for halothane 1983;62:09
- halothane, effects of deuteration 1984;63:495
- halothane MAC
    - and physostigmine in dogs 1978;57:180
    - effect of pancuronium 1979;58:497
- MAC
    - and effects of brain sodium, potassium, and osmolality 1978;57:404
    - anesthetic properties of dioxychlorane 1981;60:201
    - comparison of halothane and nitrous oxide in swine 1984;63:529
    - deliberate hypotension 1981;60:513
    - effect on sufentanil 1983;62:987
    - flurothyl 1981;60:464
    - isoflurane 1981;60:464
    - iso-Indoklon 1981;60:464
    - measurement of anesthetic potency 1981;60:380
    - nitrous oxide 1982;61:553
- properties of dioxychlorane 1981;60:201
- righting reflex, potencies of nitrous oxide in mice bred for resistance or susceptibility 1981;60:646
- thiopental, comparison with fentanyl 1983;62:151

**Pregnancy**
- abortion
    - and trace concentrations of anesthetic gases 1978;57:328
    - incidence in operating room personnel 1979;58:302
    - nitrous oxide effect on rat fetus 1980;59:175
- cerebrospinal fluid, (abstract) 1984;63:204
- differential sensitivities of nerve fibers 1983;62:1070
- endorphins, plasma and cerebrospinal fluid levels 1982;61:893
- epidural anesthesia, spread (letter) 1979;58:350
- fetal blood flow, maternal halothane anesthesia reduction, acidotic sheep fetus 1980;59:35
- fetal development, developmental toxicity of methoxyflurane in mice 1980;59:421
- halothane, effect of intrauterine exposure on postnatal autotolerance and brain weight 1983;62:565
- myasthenia gravis, anesthesia for 1978;57:441
- pulmonary venous admixture, local anesthetics and 1979;58:318
- succinylcholine, correlation of plasma cholinesterase and duration of 1977;56:78
- teratogenicity
    - and trace concentrations of anesthetic gases 1978;57:328
    - incidence in operating room personnel 1979;58:302
    - nitrous oxide effect on rat fetus 1980;59:175
    - nitrous oxide, effect on thymidine and methionine syntheses 1983;62:738
- third trimester, effects of antacid volume 1984;63:752

**Premedication**
- anticholinergic, effects on lung mechanics 1981;60:85
- anticholinergic, atropine (questions and answers) 1975;54:716
- atropine
    - alone and with morphine and scopolamine 1977;56:606
    - effects on lung mechanics 1981;60:85
    - racial mydriatic response to 1978;57:572
- atropine (questions and answers) 1975;54:716
- coma and abnormal neurologic signs following 1980;59:79
- diazepam
    - comparison with droperidol and hydroxyzine 1977;56:496
    - diazepam, droperidol, and hydroxyzine changes in airway resistance 1976;55:18
    - effect on memory and learning 1979;58:452
    - intravenous, as surgical premedicant 1977;56:211
    - plasma levels 1975;54:173
    - plus pentazocine, supplementing local analgesia 1976;55:177

**Premedication**—*continued*
  diazepam-morphine, effect on awareness and dreams, nitrous oxide anesthesia 1976;55:702
  droperidol, comparison with diazepam and hydroxyzine 1977;56:496
  glycopyrrolate
    control of gastric acidity by, in parturient 1977;56:642
    effects on lung mechanics 1981;60:85
    gastric acidity and (letters) 1979;58:157
  hydroxyzine, comparison with droperidol and diazepam 1977;56:496
  Innovar 1975;54:224
  lorazepam
    injectable 1976;55:522
    intramuscular, compared with hydroxyzine 1984;63:571
    lack of recall and relief of anxiety 1976;55:792
    versus pentobarbital 1977;56:489
  midazolam, intramuscular premedication 1982;61:933
  morphine
    alone and with scopolamine and atropine 1977;56:606
    and promethazine as intravenous premedicants 1977;56:801
    comparison with nalbuphine 1977;56:808
  nalbuphine, comparison with morphine 1977;56:808
  oral, associated with endotracheal tube obstruction 1984;63:867
  pentobarbital, lorazepam versus 1977;56:489
  promethazine, and morphine 1977;56:801
  RO 21-3981, intravenous, for premedication and anesthesia induction 1978;57:01
  scopolamine
    alone and with morphine and atropine 1977;56:606
    effect on memory and learning 1979;58:452
    racial mydriatic response to 1978;57:572
**Preservatives**, see Pharmacology
**Pressure**, see
  Airway
  Blood pressure
  Brain, intracranial pressure
  Cerebrospinal fluid
  Eye, intraocular
  Heart, atrial, ventricular
  Hyperbaria
  Hypobaria
  Lung, intravascular
  Microcirculation
  Temperature
  Temperature, vapor
  Theories of anesthesia
  Veins, venous pressure
  Ventilation, positive end-expiratory pressure
**Priapism**, see Complications
**Procaine**, see Anesthetics, local
**Progeria**, see Complications
**Promethazine**, see Ataractics, promethazine
**Propanidid**, see Anesthetics, intravenous
**Propranolol**, see
  Heart
  Sympathetic nervous system, sympatholytic agents
**Prostaglandins**, see Hormones
**Protamine**, see Blood, coagulation
**Protein**
  (abstract) 1984;63:247
  albumin, fibrinogen deficiencies associated with packed red blood cells 1975;54:89
  albumin, salt poor, in interstitial lung diseases 1979;58:13
  amino acids, effect of *d*-phenylalanine on nociceptive, flexion reflex thresholds (letter) 1983;62:857
  binding, *d*-tubocurarine, determinants in health and disease 1983;62:870
    diazepam influence on serum protein binding of bupivacaine 1984;63:980
    effects of pH on, of lidocaine 1978;57:478
    lidocaine 1981;60:395
    pancuronium, effects of age, sex, and disease on plasma binding 1983;62:29
    plasma neuromuscular relaxants 1983;62:160
  intravenous albumin, prevention of spinal hypotension, cesarean 1980;59:655
**Pseudocholinesterase**, see
  Biotransformation (drugs)
  Enzymes
  Genetic factors
**Pseudoxanthoma elastium**, see Complications
**Psychologic responses**
  comparison of ketamine and thiopental 1984;63:1087
  effect of subanesthetic concentrations of enflurane and halothane on behavior 1978;57:434
  postanesthetic 1984;63:653
  postoperative, halothane or enflurane anesthesia 1980;59:245
  trace concentrations 1979;58:475
**Publications**
  criticism in medicine 1983;62:1013
**Pulmonary**, see Lung
**Pulseless disease**, see Complications
**Pupil**, see Eye
**Pyrexia**, see Hyperthermia
**Pyridostigmine**, see Antagonists, neuromuscular relaxants
**Questions and answers**
  ASA classification 1976;55:614
  back pain, a contraindication to spinal anesthesia 1975;54:505
  balanced anesthesia 1976;55:907
  breathalyzer test, and exposure to anesthetic gases 1976;55:615
  congenital abnormality in the children of exposed OR personnel 1976;55:760
  endotracheal tubes 1975;54:715
  epidural antibiotics, with prolonged catheterization 1976;55:132
  filters used during massive blood transfusions 1975;54:45
  gag reflex 1976;55:461
  heparinization, operative 1975;54:506
  humidity in operating rooms 1976;55:134
  intrathecal cold saline solution, for intractable pain 1976;55:131
  laryngoscope bulb, electrical hazard 1975;54:505
  management of patient with hypokalemia on diuretic therapy 1976;55:276
  myasthenia gravis, use of ester-type local anesthetic 1975;54:506
  $NaHCO_3$ use, with the administration of bank blood 1976;55:274
  peripheral nerve stimulator 1975;54:297
  physician–patient relationship, legal aspects of anesthesia 1976;55:463
  pre- and post-anesthetic use of atropine, in patients with glaucoma 1976;55:460
  premedication, atropine 1975;54:716
  preoperative blood volume determination 1976;55:275
  regional versus general anesthesia 1976;55:277
  safety in operation of rechargeable ECG monitor (Tektronix) 1976;55:613
  succinylcholine, avoidance of side effects 1975;54:637
  terminology and definition of word "metabolism" 1976;55:760
  terminology in anesthesia 1975;54:640
  "Torr", origin of the word 1976;55:131
  use of electrocautery, during operation following ether skin prep 1975;54:210
  ventilating systems in operating rooms 1975;54:297
**Race**, see Genetic factors
**Radial artery**, see Arteries
**Radiation**, see Complications
**Ranitidine**, see
  Gastrointestinal tract, stomach
  Histamine
  Pharmacology
**Recall**, see Memory
**Receptors**
  adrenergic
    and others 1979;58:510
    halothane–epinephrine arrhythmias 1984;63:297
    trimethaphan-induced vasodilation 1984;63:290
  β-adrenergic, effect of halothane in canine myocardium 1981;60:401

carotid body, chemodectoma diagnosed by hypertension and tachycardia during anesthesia 1980;59:388
chemoreceptors
carotid body, hypoxic ventilation 1984;63:106
respiratory depression following bilateral carotid end-arterectomy 1981;60:64
$H_2$, ranitidine, and Mendelson's syndrome 1982;61:130
opiate 1984;63:143
narcotic dosage and CNS receptor binding 1983;62:705
role in anesthesiology 1980;59:874
opioid, anesthetic potency of nalbuphine 1981;60:629
pressoreceptors, baroreceptor reflexes and pulmonary hemodynamics during halothane and halothane nitrous oxide anesthesia 1981;60:701
presynaptic muscarinic 1984;63:1059
**Records, anesthesia**
auditing of performance 1980;59:465
computerized, patient evaluation 1983;62:198
preoperative, summary of patients' historical information, preanesthesia visit 1980;59:03
PSRO system for anesthesiologists 1977;56:16
**Recovery** 1980;59:431
ketamine 1975;54:169, 312
measurement, from general anesthesia 1979;58:324
psychomotor tests 1984;63:653
**Recruitment,** see Manpower
**Reflexes**
baroreceptor
(abstract) 1984;63:237
control of heart rate by epidural anesthesia 1983;62:815
during halothane and halothane-nitrous oxide anesthesia in the dog 1981;60:701
see
Eye
Receptors
**Regurgitation,** see Gastrointestinal tract, stomach
**Relaxants,** see Neuromuscular relaxants
**Renal,** see Kidney
**Renin,** see
Hormones
Polypeptides
**Research**
criticism, in medicine 1983;62:1013
ethics, hazards of ketamine in ischemic heart disease (letter) 1983;62:1044
laboratory, closed system for biochemical experiments, volatile anesthetics 1981;60:435
replication may be subject specific (letter) 1983;62:617
**Reserpine,** see Ataractics, rauwolfia
**Residents,** see
Education
Manpower, recruitment
**Resistance,** see
Airway
Blood pressure, peripheral vascular resistance
Blood, viscosity
Electrical systems
Lung
**Respiration,** see
Metabolism, oxygen consumption
Oxygen, consumption
Ventilation
**Respiratory distress syndrome,** see Lung
**Respirometry**
noninvasive assessment, extubation 1975;54:807
**Resuscitation,** see
Anesthesia, obstetric
Complications, cardiac arrest
Complications, respiratory
Heart, massage
Shock
Transfusion
Ventilation, artificial
**Retrolental fibroplasia,** see Eye
**Reversal,** see Antagonists
**Rheology,** see Blood
**Risk**
estimate
in open heart surgery with cardiopulmonary bypass 1981;60:623
preoperative in cardiac surgery 1981;60:625
physical status classification (questions and answers) 1976;55:614
**Ritodrine,** see Pharmacology
**Romano-Ward syndrome,** see Complications
**Scavengers,** see Equipment, exhaust systems
**Scheduling,** see Anesthesia, scheduling
**Sciatic nerve block,** see Anesthetic techniques, regional
**Scopolamine,** see
Parasympathetic nervous system, premedication
Premedication
**Secobarbital,** see Hypnotics, barbiturate
**Seizures,** see
Brain
Complications
Toxicity
**Serotonin**
antagonism, endotoxic shock (abstract) 1982;61:204
ketanserin for treatment of postoperative hypertension 1983;62:63
pain and CNS serotonin 1981;60:854
postoperative hypertension, coronary artery bypass surgery (abstract) 1982;61:216
pulmonary uptake, inhibition of 5-hydroxytryptamine removal by free radicals 1982;61:666, 671
**Servo systems,** see
Anesthetic techniques
Equipment
**Sevoflurane,** see Anesthetics, Volatile
**Shock**
catechol response, blood flow effects (abstract) 1982;61:210
circulatory, diagnosis and fluid treatment of 1979;58:124
resuscitation, after intratracheal epinephrine 1984;63:829
secondary to hypokalemia and hypocalcemia from enemas 1981;60:762
**Shunt,** see
Lung, oxygen gradients
Oxygen
Surgery, neurological
Ventilation
**Sickle cell disease,** see Blood
**Skin**
color, cyanosis of upper extremities and vasodilation of lower limbs 1981;60:453
transcutaneous oxygen tension, trend indicator of arterial $Po_2$ 1982;61:252
wound healing, in presence of nitrous oxide in rats 1978;57:527
**Sodium,** see Ions
**Solubility**
blood, estimation (brief reports) 1976;55:593
blood, hematocrit effects on volatile anesthetics 1984;63:911
blood-gas partition coefficient enflurane 1982;61:1006
inhalation anesthetics, increase in uptake, excretion, and blood solubility after eating, in man 1978;57:224
oil, anesthetic properties of dioxychlorane 1981;60:201
partition coefficients
anesthetic properties of dioxychlorane 1981;60:201
local anesthetics 1982;61:56
water, anesthetic properties of dioxychlorane 1981;60:201
**Somato-sensory evoked responses,** see
Brain, evoked potentials
Monitoring, evoked potentials
**Specific gravity,** see Physics
**Spectrometry,** see Measurement techniques
**Sphygmomanometer,** see Equipment
**Spinal accessory nerve,** see Nerve
**Spinal anesthesia,** see Anesthetic techniques, spinal
**Spinal cord**
diazepam, effects on evoked electrospinogram and evoked electromyogram 1981;60:197

**Spinal cord**—*continued*
  injuries, anesthesia and autonomic hyperreflexia 1982;61:344
  intraoperative function, monitoring using hypnosis 1976;55:42
  stimulation, facilitation of primary afferent depolarization 1982;61:410
  subarachnoid steroids 1978;57:313
**Statistics**
  computer assisted patient evaluation 1983;62:198
  interpretation of negative results (letter) 1983;62:1045
  (letter) 1984;63:1050
  mean pH values, hydrogen ion concentration versus 1979;58:487
  medical 1976;55:82, 357, 846
  methods
    linear regression (letter) 1982;61:956
    postanesthetic hepatic injury (letter) 1982;61:718
    question of (correspondence) 1977;56:467
    Student's *t*-test (questions and answers) 1977;56:596
    variation as key to research design 1978;57:322
  morbidity and mortality 1984;63:789
  pH data
    analysis (correspondence) 1978;57:143
    calculation (letter) 1979;58:63
    central tendency and the mean of mean (editorial) 1979;58:01
  statistical pearls
    I. an empty shell game 1976;55:82
    II. how often did that happen? 1976;55:357
    III. the most likely interpretation 1976;55:846
**Stellate ganglion,** see
  Anatomy
  Anesthesia, diagnostic, therapeutic
  Anesthetic techniques, regional
  Heart
  Sympathetic nervous system, ganglia
**Sterilization**
  ethylene oxide, of spinal anesthesia ampules (questions and answers) 1977;56:743
  laparoscopic, "pentazepam" 1976;55:177
  skin
    warming povidone-iodine solution for (correspondence) 1978;57:142
    warming preparation solutions (correspondence) 1977;56:748
**Steroids,** see
  Anesthetics, intravenous
  Hormones, adrenal
**Stethoscope,** see Equipment
**Stimulator,** see
  Equipment
  Monitoring
  Nerve
  Neuromuscular transmission
**Stomach,** see Gastrointestinal tract
**Streptomycin,** see Antibiotics
**Students,** see Education
**Stylet,** see Equipment
**Stylets,** see Equipment
**Subarachnoid space,** see
  Anatomy
  Spinal cord
**Subclavian vein,** see Veins
**Subdural space,** see
  Anatomy
  Anesthetic techniques, spinal, epidural
**Succinylcholine,** see Neuromuscular relaxants
**Sufentanil,** see
  Analgesics
  Anesthetics, intravenous
**Surgery**
  adenotonsillectomy, periodic apnea during 1979;58:50
  cardiovascular
    anesthetic management of the first permanent, orthotopic, prosthetic cardiac replacement 1984;63:685
    anticoagulant monitoring and neutralization during open heart surgery 1983;62:1095
    aortic valve replacement, hemodialysis-dependent patient, anesthetic considerations 1975;54:24
    artificial heart implantation, cardiovascular and respiratory effects of isoproterenol 1976;55:560
    assessment and reversal of heparin-induced anticoagulation for cardiopulmonary bypass 1983;62:710
    blood clot formation during bypass, procedures necessitated by massive hemorrhage 1978;57:273
    cardiopulmonary bypass, effect of $PaCO_2$, on $O_2$ consumption 1976;55:269
    comparison of lidocaine and morphine as adjunct to anesthetic 1980;59:130
    control of hypertension during bypass, with cryptenamine 1978;57:54
    criteria for early extubation after 1977;56:703
    damage following bypass, with halothane 1977;56:556
    direct ventricular fibrillation 1984;63:743
    dobutamine and myocardial metabolism 1982;61:917
    effect of heated humidified gases on temperature drop 1984;63:1106
    effect of protamine 1981;60:33
    effect of protamine administration 1983;62:831
    facial paleness (letter) 1982;61:475
    factors affecting A-$aDO_2$ after open-heart surgery 1976;55:315
    following propranolol 1975;54:571
    halothane blood solubility during bypass, with crystalloid hemodilution and hypothermia 1977;56:622
    heart failure after cardiopulmonary bypass (case history) 1975;54:842
    hemodynamic effects of morphine 1976;55:47
    hemodynamic tracking system 1980;59:169
    hemodynamics after aortic valve replacement (abstract) 1981;60:263
    hemodynamics of intravenous nitroglycerin 1982;61:927
    human factors and tasks in anesthesia 1976;55:378
    hypotension following 1982;61:387
    hypotension following bypass 1977;56:720
    infants 1975;54:800
    intra-aortic balloon counterpulsation for right heart failure 1980;59:74
    monitoring of femoral artery pressure during replacement of aneurysm of descending thoracic aorta 1977;56:603
    neuropsychiatric complications of bypass 1982;61:903
    nitroglycerin and myocardial metabolism 1982;61:828
    pediatric anesthetic complications 1984;63:657
    pericardectomy 1976;55:378
    percutaneous, transluminal coronary angioplasty (abstract) 1981;60:280
    perfusion characteristics during bypass and subsequent changes in alveolar–arterial oxygen tension gradients 1978;57:298
    plasma heparin activity and antagonism during bypass with hypothermia 1977;56:564
    platelet involvement in coagulation time 1984;63:394
    postoperative complications following carotid endarterectomy (abstract) 1981;60:236
    preoperative estimation of risk 1981;60:625
    preoperative evaluation and preparation 1976;55:618
    propranolol and circulatory responses 1981;60:579
    pulmonary edema following bypass 1978;57:367
    renal function and stress response during halothane or fentanyl anesthesia 1981;60:552
    responses to clamping of the aorta during anesthesia 1979;58:372
    systemic vascular resistance in (abstract) 1982;61:181
    urine sodium and potassium during (abstract) 1980;59:526
    valve prosthesis management of a parturient 1976;55:214

  - carotid endarterectomy, complications of 1982;61:631
  - chemodectoma, hypertension and tachycardia during anesthesia 1980;59:388
  - dental
    - cannabinol during oral surgery, cardiovascular effects 1976;55:203
    - catecholamine response to oral surgery 1984;63:640
    - intravenous sedation, local anesthesia 1980;59:775
  - gastrointestinal
    - jejunolleal bypass, postoperative alveolar-oxygen tension difference 1975;54:433
    - jejunolleal shunt, anesthesia for 1975;54:65
  - gynecologic, bupivacaine vs etidocaine for vaginal delivery 1975;54:250
  - laparoscopy
    - acute hypotension 1975;54:142
    - carbon dioxide embolism during 1977;56:650
    - evanescent nitrous oxide pneumothorax 1983;62:1121
    - gas embolism death after 1978;57:232
    - rheumatoid arthritis, cricoarytenoid joints 1975;54:742
    - sterilization, "pentazepam" supplementing local analgesia 1976;55:177
    - teflon injection, vocal cords 1975;54:739
    - with local anesthesia, complications and blood-gas changes 1977;56:335
  - laryngoscopy
    - $CO_2$ laser, larynx and trachea (brief reports) 1976;55:146
    - fire hazards using $CO_2$ laser 1981;60:885
    - increased cerebrospinal fluid pressure 1975;54:687
    - intravenous procaine as supplement to general anesthesia 1979;58:492
    - maxillary sinusitis, nasotracheal intubation (brief reports) 1976;55:885
    - metal endotracheal tubes 1980;59:789
    - otolaryngologic 1984;63:368
  - maxillofacial, anesthetic hazard 1980;59:150
  - mediastinoscopy
    - innominate artery compression, simulating cardiac arrest 1976;55:748
    - laceration of left pulmonary artery during 1977;56:226
    - right radial artery pressure, during 1979;58:428
  - neurologic
    - air encephalography, simplified technique (correspondence) 1977;56:469
    - anesthesia for sitting position (correspondence) 1977;56:325
    - anesthesia for transsphenoidal, of hypophyseal region 1978;57:206
    - cardiovascular and cation effects of urea 1981;60:641
    - cerebrospinal fluid pressure, oxygen encephalography 1976;55:849
    - computerized EEG analysis 1983;62:186
    - cordotomy 1984;63:1036
    - encephalography, gas embolism (case history) 1976;55:141
    - lateral sitting position 1976;55:326
    - neuromuscular blockade, associated with trimethaphan 1976;55:353
    - nitrous oxide encephalography, pediatrics 1976;55:402
    - prevention of blood pressure response in 1979;58:241
    - somatosensory-evoked potentials 1982;61:879
    - subarachnoid intracranial pressure, anesthesia 1975;54:494
  - ophthalmologic
    - corneal abrasion, anesthesia 1975;54:465
    - intraocular pressure, thiopental and succinylcholine 1975;54:471
    - intraocular pressure during anesthesia, electroshock therapy 1975;54:479
    - ketamine, and intraocular pressure in children 1976;55:773
    - myocardial infarction following local anesthesia 1980;59:257
    - pre- and post-anesthetic use of atropine, in patients with glaucoma (questions and answers) 1976;55:460
    - vitrectomy 1975;54:58
  - orthopedic
    - blood loss control, total hip arthroplasty 1975;54:641
    - blood volume changes, total hip arthroplasty 1975;54:391
    - continuous opioid infusion for scoliosis fusion surgery 1983;62:841
    - fentanyl–morphine effects on somatosensory cortical-evoked potentials 1984;63:833
    - Harrington procedure, intraoperative monitoring 1976;55:42
    - intraoperative awakening for early recognition of possible neurologic sequelae, during Harrington-rod spinal fusion 1976;55:526
    - methylmethacrylate safety (abstract) 1980;59:542
    - monitoring intraoperative spinal cord function 1976;55:42
    - operative blood loss, total hip replacement 1975;54:641
    - sodium nitroprusside-induced hypotension 1976;55:654
    - spinal anesthesia for lumbar disc surgery 1976;55:550
    - wake-up technique to avoid neurologic sequelae during Harrington rod procedure 1977;56:733
  - pediatric
    - anesthetic complications with congenital heart disease 1984;63:657
    - fentanyl–air–oxygen anesthesia for ligation of patent ductus arteriosus in preterm infants 1981;60:331
  - pheochromocytoma 1983;62:100
    - and cesarean section, anesthesia for 1978;57:276
    - enflurane anesthesia for removal of 1977;56:62
    - isoflurane anesthesia 1975;54:419
    - isoflurane for resection of (letter) 1983;62:955
    - pulmonary artery pressure, monitoring 1983;62:1129
    - pulmonary wedge pressure, aortography 1980;59:154
  - plastic, general anesthesia technique 1976;55:165
  - plastic, larynx and trachea, carbon dioxide laser microsurgery (brief reports) 1976;55:146
  - thoracic
    - circulatory collapse after pneumonectomy 1977;56:451
    - endobronchial intubation, intraoperative protection 1976;55:340
    - high-frequency positive-pressure ventilation in open-chest surgery 1981;60:324
    - mediastinoscopy, innominate artery compression simulating cardiac arrest 1976;55:748
    - precordial ECG lead (brief reports) 1976;55:740
    - thoracotomy (brief reports) 1976;55:740
    - oxygen-jet ventilation during reconstruction in patients with tracheal stenosis 1977;56:429
    - precored ECG lead, chest operations (brief reports) 1976;55:740
    - stenotic trachea 1976;55:191
  - thymectomy 1976;55:13
  - transplantation, liver 1984;63:1131
  - urologic
    - independent plasma levels of glycine and sodium (abstract) 1983;62:291
    - neck pain, bladder perforation 1980;59:801
    - prevention of hypothermia during cystoscopy in neonates (brief reports) 1976;55:592
  - wound healing, in presence of nitrous oxide in rats 1978;57:527

- **Swan-Ganz**, see
  - Equipment, catheters, flow-directed
  - Monitoring, vascular
- **Sympathetic blockade** 1975;54:593

**Sympathetic nervous system**

- adrenergic nerve ending 1984;63:1059
- adrenergic receptors, clonidine reduction of halothane 1982;61:741
- alpha-adrenergic agonists, clonidine, halothane safety and (abstract) 1982;61:173
- alpha-adrenergic antagonists, labetalol, postoperative hypertension (abstract) 1982;61:195
- anesthesia
  - catecholamines and hemodynamics, autonomic dysfunction 1982;61:701
  - effects of halothane, thiamylal, and ketamine 1983;62:129
- anesthesia (letter) 1984;63:371
- $\beta$-adrenergic antagonists (abstract) 1983;62:282
- $\beta$-adrenergic blockade, cardiac effects 1984;63:817
- beta-adrenergic blocking agent, propranolol in cardiac surgery 1975;54:571
- catecholamines
  - blood levels, after administration of naloxone 1982;61:349
  - effect of succinylcholine on plasma levels 1983;62:627
  - enflurane compared to fentanyl anesthesia (abstract) 1980;59:532
  - epinephrine, catecholamine release with morphine and diazepam 1981;60:406
  - fentanyl-$O_2$ anesthesia 1981;60:563
  - halothane–epinephrine arrhythmias 1984;63:297
  - norepinephrine, catecholamine release with morphine and diazepam 1981;60:406
  - norepinephrine, effect of fentanyl on canine coronary arteries 1981;60:21
  - plasma levels (letter) 1982;61:366, 384
- dobutamine, myocardial metabolism 1982;61:917
- dopamine
  - arrhythmic doses of, and epinephrine, during halothane, enflurane, methoxyflurane, and fluroxene anesthesia in goats 1977;56:207
  - hypoxic ventilation 1984;63:106
  - renovascular effects (abstract) 1980;59:552
- dystrophy
  - centrally induced, of upper extremity 1978;57:373
  - reflex sympathetic, in a 6-year-old, treatment by transcutaneous nerve stimulation 1977;56:438
  - treatment with regional intravenous reserpine 1980;59:500
  - volitional sympathetic control 1980;59:785
- ephedrine, activity in the pregnant ewe (abstract) 1981;60:278
- epinephrine
  - arrhythmias induced by, during enflurane anesthesia, protection from lidocaine 1978;57:547
  - arrhythmic doses of, and dopamine, during halothane, enflurane, methoxyflurane, and fluroxene anesthesia in goats 1977;56:207
  - effects of intratracheal administration during cardiopulmonary resuscitation 1984;63:829
  - enflurane, isoflurane, and halothane, comparative interaction in man 1976;55:709
  - injection, ventricular arrhythmias, 1975;54:468
  - interactions, further data on (correspondence) 1977;56:468
  - interactions of (correspondence) 1977;56:747
  - plasma levels during anesthesia 1982;61:366
  - plasma lidocaine concentrations following epinephrine–lidocaine injection 1978;57:724
  - spinal anesthesia and 1982;61:746
  - spinal cord effects (letter) 1981;60:913
  - suppression of noxiously evoked dorsal horn neuron activity (abstract) 1983;62:253
- ganglia, $\alpha$-adrenergic blocking by trimethaphan 1984;63:290
- ganglionic blocking agents, lack of CNS depression from large doses of trimethaphan 1977;56:06
- Horner's syndrome, following obstetric extradural block 1980;59:299
- ketamine 1980;59:45
- levodopa, effect on halothane anesthesia 1975;54:178
- local anesthetics, vascular smooth muscle 1982;61:756
- metoprolol, long-term therapy and neuroleptanesthesia in coronary artery surgery 1983;62:380
- norepinephrine, plasma levels during anesthesia 1982;61:366
- paravertebral sympathetic block, with bupivacaine, analgesia for labor 1978;57:486
- propranolol
  - attenuates renin release 1981;60:569
  - control of rate-pressure product, cardiac anesthesia (abstract) 1981;60:274
  - effects on circulatory responses to induction of diazepam–nitrous oxide anesthesia and to endotracheal intubation 1981;60:579
  - levels during cardiac surgery (abstract) 1981;60:239
  - membrane-stabilizing actions and 1981;60:897
  - perioperative hypoglycemia 1983;62:1035
  - rate–pressure product, cardiac anesthesia 1981;60:732
- receptors, adrenergic and others 1979;58:510
- splanchnic block, study of technique and spread of solution 1981;60:369
- sympathetic agents
  - propranolol and circulatory responses 1981;60:579
  - propranolol, and isoproterenol effect on halothane MAC 1976;55:383
  - propranolol, cardiac surgery 1975;54:571
  - propranolol, surgical anesthesia 1976;55:1
- sympatholytic agents 1984;63:365
  - cryptenamine, control of hypertension during cardiopulmonary bypass with 1978;57:54
  - effect of propranolol, circulatory responses, diazepam–nitrous oxide induction and intubation (abstract) 1981;60:265
  - hemodynamic effects of metocurine in patients with coronary artery disease receiving 1977;56:255
  - levels during cardiac surgery (abstract) 1981;60:239
  - local anesthetics 1981;60:897
  - propranolol anesthetics and 1977;56:283
  - propranolol attenuates renin release 1981;60:569
  - propranolol, effect on hemodynamic response and blood cyanide levels 1979;58:466
  - propranolol for ischemic myocardium 1982;61:10
- beta-adrenergic blocking agent
  - propranolol in cardiac surgery 1975;54:571
  - timolol-induced bradycardia 1980;59:301
  - use of propranolol to control rate–pressure product during cardiac anesthesia (abstract) 1981;60:274
- sympathomimetic agents
  - action of tetrodotoxin 1976;55:568
  - activity of ephedrine in the pregnant ewe (abstract) 1981;60:278
  - cardiovascular and respiratory effects of esoproterenol, artificial heart implantation 1976;55:560
  - ephedrine, cesarean section 1982;61:839
  - phenylephrine, pharmacokinetics and neural blockade after livocaine 1984;63:129
  - vasopressors, effect on spinal anesthesia 1975;54:455
- transcutaneous electrical stimulation, increased skin temperature during 1980;59:22

- **Synapses,** see
  - Anatomy
  - Brain
  - Neuromuscular junction
  - Spinal cord
  - Sympathetic nervous system
- **Syringes,** see Equipment
- **Systolic time intervals,** see Heart
- **Tachyphylaxis,** see Pharmacology
- **Tamponade,** see
  - Complications
  - Heart
- **Tearing,** see Eye
- **Teeth,** see
  - Anesthesia, dental
  - Complications, dental
  - Pain, experimental
- **Telogen effluvium,** see Complications
- **Temperature**
  - body, effect of halothane and fentanyl on temperature gradients 1983;62:1002
  - body, maintenance by heated humidification 1976;55:719
    - heated and humidified gas effects (letter) 1982;61:393
    - humidification and adult body temperature during general anesthesia 1981;60:736
    - intraoperative 1983;62:211
    - measurements of 1982;61:284
    - operating room (letter) 1981;60:226
    - operating room temperature effects 1980;59:852
    - operating room temperature effects (abstract) 1980;59:557
    - operating room temperature important to infants and children (letter) 1981;60:169
  - body rewarming, effect of heated humidified gases 1984;63:1106
  - cold agglutination 1984;63:349
  - dissociation constants, local anesthetics 1983;62:1025
  - inspired air with immersion heater humidifiers 1976;55:331
  - measurement 1979;58:351
    - liquid crystal thermometry (letter) 1982;61:803
  - monitoring
    - intraoperative 1983;62:211
    - liquid-crystal thermometry as screening device for intraoperative hyperthermia 1978;57:669
  - neuromuscular relaxants
    - *d*-tubocurarine and pancuronium, reaction to 1981;60:18
    - potency of *d*-tubocurarine and pancuronium (letter) 1981;60:455
  - postoperative, relationship of age, anesthesia, and shivering to rewarming in adults 1981;60:746
  - production, striated muscle of frogs 1975;54:527
  - regulation, thermoregulatory defect in rats during anesthesia 1977;56:09
  - specific gravity, normal human cerebrospinal fluid and tetracaine density 1981;60:814
- **Teratogenicity,** see
  - Pregnancy
  - Toxicity
- **Terbutaline,** see Pharmacology
- **Tetracaine,** see Anesthetics, local
- **Tetrodotoxin,** see Anesthetics, local
- **THAM,** see Acid-base equilibrium, THAM
- **Theophylline,** see Pharmacology
- **Theories of anesthetic action**
  - anesthetic potencies and theories of narcosis (abstract) 1980;59:535
  - electron mobility 1983;62:936
  - lipid solubility
    - anesthetic properties of dioxychlorane 1981;60:201
    - convulsant gases and anesthetics 1981;60:464
  - pressure reversal, nonlinear antagonism in mice 1979;58:19
  - anesthetic potencies and theories of narcosis (abstract) 1980;59:535
  - review of molecular mechanisms 1984;63:929
- **Thiamylal,** see Anesthetics, intravenous
- **Thiomethoxyflurane,** see Anesthetics, volatile
- **Thiopental,** see Anesthetics, intravenous
- **Thoracic surgery,** see Surgery, thoracic
- **Thoracotomy,** see Anesthesia, thoracic
- **Thromboembolism,** see Embolism
- **Thyroid,** see Hormones
- **Tidal volume,** see
  - Lung
  - Ventilation
- **Timolol,** see
  - Eye, intraocular pressure
  - Sympathetic nervous system, sympatholytic agents
- **Tobramycin,** see Antibiotics
- **Tolerance**
  - halothane, effect of intrauterine exposure on postnatal autotolerance and brain weight 1983;62:565
  - nitrous oxide, compared to barbiturates in mice 1981;60:137
  - to ketamine 1976;55:788
- **Tomography,** see Measurement techniques
- **Tongue,** see Airway
- **Topical anesthesia,** see
  - Anesthetics, local, lidocaine
  - Anesthetic techniques
- **Toxicity**
  - bleomycin (abstract) 1984;63:274
  - bupivacaine, successful resuscitation 1984;63:856
  - carcinogenicity, test of, and enflurane, isoflurane, halothane, methoxyflurane, and nitrous oxide in mice 1978;57:678
  - chloroprocaine (letter) 1984;63:544
  - cyanide
    - during nitroprusside therapy in oliguric patient 1977;56:729
    - failure to antagonize nitroprusside 1980;59:672
    - limitations for use in plasma and whole blood 1979;58:457
    - prevention with thiosulfate 1982;61:120
  - enflurane, reproductive toxicity 1982;61:19
  - fluroxene 1976;55:529
  - halothane, hepatic injury 1982;61:824
  - hepatic 1983;62:155
    - cellular concentrations of anesthetic (letters) 1979;58:259
    - effect of halothane, isoflurane, and blood loss 1984;63:965
    - halothane 1982;61:809
    - responses to volatile anesthetics: changes in surface scanning and enzyme leakage 1978;57:605
  - inhalation anesthetics
    - review of (correspondence) 1978;57:595, 596
    - trace concentrations 1978;57:328
  - local anesthetics
    - 2-chloroprocaine-CE and bupivacaine 1982;61:279
    - bupivacaine, cardiotoxicity compared to lidocaine 1984;63:549
    - cardiovascular effects of convulsant and supraconvulsant doses 1982;61:03
    - cell membrane fusion by chloroprocaine 1984;63:985
    - chloroprocaine and bupivacaine in mice (letter) 1981;60:455
    - comparative CNS toxicity following rapid intravenous administration 1983;62:375
    - cytotoxicity of (letter) 1981;60:168
    - damaged muscle fiber regeneration 1980;59:727
    - deaths from convulsions in mice 1980;59:401
    - effects of epinephrine (letter) 1984;63:702
    - evaluation of the myotoxicity of bupivacaine in bier block 1983;62:796
    - in vivo study 1982;61:961
    - influence of lidocaine and bupivacaine on atria 1984;63:01
    - inhibit hydrolysis of chloroprocaine by human serum 1978;57:534
    - inject route alteration 1980;59:925
    - intravenous amide 1982;61:317
    - lidocaine, cardiotoxicity compared to bupivacaine 1984;63:549
    - mepivacaine (carbocaine) in rat 1980;59:275
    - myotoxicity of lidocaine in rats and humans 1981;60:471
    - neurologic deficits following epidural or spinal anesthesia 1981;60:150

**Toxicity**—*continued*
- local anesthetics—*continued*
  - neurotoxicity after injection of large volumes 1983;62:802
  - reverse arterial blood flow as a pathway for 1978;57:428
  - systemic 1978;57:387
- methoxyflurane, fetal development in mice 1980;59:421
- methylene blue injection, renal blood flow 1976;55:674
- mutagenicity, halothane 1979;58:64
- neurotoxicity, responses to hypoosmotic solutions 1982;61:912
- nitrous oxide
  - effect on thymidine and methionine syntheses 1983;62:738
  - exposure to and neurologic disease among dental professionals 1981;60:297
- oxygen (case history) 1976;55:588
- renal, anesthetics 1982;61:812
- teratogenicity, and trace concentrations of anesthetic gases 1978;57:328
- trace concentrations, nitrous oxide effect on rat fetus 1980;59:175
- trace concentrations (abstract) 1981;60:281

**Trace concentrations,** see
- Anesthetics, gases, tract concentrations
- Anesthetics, volatile, trace concentrations
- Toxicity

**Trachea,** see Lung

**Tracheal tubes,** see Equipment, endotracheal tubes

**Tracheotomy,** see
- Equipment
- Surgery
- Ventilation, artificial

**Train-of-four,** see Neuromuscular relaxants
- Measurement techniques, neuromuscular blockade
- Neuromuscular relaxants measurement of response

**Tranquilizer,** see
- Ataractics
- Hyprotics

**Transcutaneous,** see
- Measurement techniques, blood gases
- Nerve, stimulation

**Transducers,** see Equipment

**Transfusion** 1983;62:122
- (abstract) 1984;63:234
- anemia, management of blood loss 1979;58:439
- auto, hemotherapy transfusion 1982;61:618
- autotransfusion, Haemonetic's Cell-Saver (abstract) 1981;60:242
- complications, wrong blood as cause of death 1981;60:777
- fibrinogen and albumin deficiencies associated with packed red blood cells 1975;54:89
- filters, evaluation of 1978;57:463
- hemolysis, mechanical effects on packed erythrocyte transfusion 1982;61:776
- intraoperative blood replacement (brief reports) 1975;54:550
- method for massive fluid resuscitation in the trauma patient 1983;62:613
- packed red cell 1975;54:89
- potassium, acute hyperkalemia associated with massive blood replacement (letter) 1983;62:1044
- stored blood
  - correlation of ionized calcium citrate, and hydrogen ion concentration 1979;58:274
  - plasma cholinesterase activity in 1980;59:211
  - rapid warming causes bubbles in intravenous tubing 1980;59:512
  - rupture of pressurized plastic bags (letter) 1980;59:228
- use of blood components 1975;54:01

**Transplantation,** see
- Individual procedures
- Organs
- Surgery, individual procedures and organs

**Transsphenoidal surgery,** see Surgery, neurologic

**Transtracheal,** see
- Anesthetic techniques
- Larynx
- Ventilation

**Trendelenburg,** see Position

**Trichloroethylene,** see Anesthetics, volatile

**Tricyclic antidepressants,** see Ataractics

**Trigger points,** see Pain

**Trimethaphan,** see
- Anesthetic techniques, hypotensive
- Sympathetic nervous system, ganglia

**Tris,** see Acid-base equilibrium, THAM

**Tubes, endotracheal,** see Equipment, endotracheal tubes

**Tubocurarine,** see
- Neuromuscular relaxants, *d*-tubocurarine

**Twins,** see Anesthesia, obstetric, pediatric

**Ultrasound,** see Measurement techniques

**Ultraviolet,** see Measurement techniques

**Uptake,** see
- Induction
- Pharmacokinetics

**Urine,** see Kidney

**Urology,** see Surgery, urologic

**Urticaria,** see Complications

**Uterus**
- blood flow, nitroglycerine therapy for hypertension, pregnant ewes 1980;59:494
- contractility, and enflurane, in rabbits 1978;57:160
- rupture, with the use of vaginal prostaglandin $E_2$ suppositories (letter) 1983;62:1046

**Uvula,** see Airway, obstruction

**Vaginal delivery,** see Anesthesia, obstretric

**Vancomycin,** see Antibiotics

**Vapor pressure,** see Physics

**Vaporizers,** see Equipment, vaporizers

**Vasopressin,** see Hormones

**Vasopressors,** see Sympathetic nervous system, sympathomimetic agents

**Vecuronium,** see Neuromuscular relaxants

**Veins**
- air embolism, prophylaxis 1975;54:792
- basilic vein versus jugular technique CVP catheter positioning (brief reports) 1975;54:696
- cannulation
  - bilateral thrombosis of 1981;60:448
  - fiberoptic transillumination for 1981;60:348
  - (letter) 1984;63:373, 1143
  - straight vs J-wire (abstract) 1981;60:275
- central venous catheters, tip migration 1984;63:949
- internal jugular, cannulation, ultrasound-simulated techniques 1984;63:673
- jugular
  - bilateral thrombosis of 1981;60:448
  - cannulation 1982;61:536
  - cannulation, comparison of internal and external routes 1980;59:40
  - cannulation, errant guide wire (letter) 1982;61:394, 717
  - cannulation, hydrohemothorax following, recognized by intravenous pyelography 1978;57:507
  - cannulation, time required 1983;62:97
  - external cannulation (abstract) 1981;60:275
  - location with ultrasound Doppler blood flow detector 1978;57:118
- venipuncture, central venous pressure (brief reports) 1975;54:157
- versus basilic vein technics, CVP catheter positioning (brief reports) 1975;54:696
- pulmonary admixture, changes in oxygen 1976;55:693
- subclavian, lymph leakage following catheterization of 1978;57:123
- vena cava, superior vena caval obstruction during heart surgery 1983;62:941
- venous pressure, noninvasive method for measuring during general anesthesia 1981;60:901

**Vena cava,** see
- Anatomy
- Veins

**Venous pressure,** see Veins

**Ventilation**
- alveolar oxygen tension
  - calculation (correspondence) 1978;57:746
  - alveolar-arterial oxygen tension difference 1975;54:433
  - factors affecting, open heart surgery 1976;55:315
- alveolar, noninvasive measurement of gas exchange 1980;59:263
- apnea
  - atypical pseudocholinesterase 1976;55:243
  - during adenotonsillectomy 1979;58:50
  - maintenance of consciousness with 1979;58:52
  - postoperative, covert seizures as cause of 1978;57:136
- prolonged, succinylcholine (case history) 1976;55:737
- artificial
  - early extubation vs prophylactic ventilation in high risk patient 1981;60:76
  - manually operated self-inflating resuscitation bags 1977;56:202
  - tracheobronchial cytologic changes 1980;59:759
  - tracheotomy (letter) 1984;63:1142
- carbon dioxide, effects of enflurane during spontaneous ventilation 1978;57:610
- carbon dioxide response, effect of epidural morphine 1983;62:633
- carbon dioxide tension, during anesthesia 1983;62:1065
- cardiovascular anomaly 1976;55:481
- Cheyne-Stokes, fluctuating intracranial hypertension due to 1977;56:216
- congenital lobar emphysema (case history) 1976;55:869
- continuous positive pressure
  - and positive end-expiratory pressure, cardiopulmonary effects 1977;56:633
  - cardiopulmonary effects of, and positive end-expiratory pressure (special correspondence) 1978;57:346, 347
  - effects on carotid flow during cardiopulmonary resuscitation, dogs 1982;61:557
- controlled, cardiovascular effects 1975;54:701
- COPD, enflurane anesthesia 1976;55:806
- dead space, measurement techniques, mechanical ventilators 1980;59:488
- dextran 40 anaphylaxis (editor's choice) 1975;54:736
- diazepam, or droperidol, respiratory function following premedication with 1978;57:695
- droperidol, or diazepam, respiratory function following premedication with 1978;57:695
- *d*-tubocurarine 1983;62:809
- effects of intraoperative PEEP, on postoperative arterial oxygenation 1975;54:427
- enflurane, ventilatory depression by, during clinical anesthesia 1980;59:103
- extracorporeal $CO_2$ removal and 1978;57:470
- foot pedal control, bronchoscopy (brief reports) 1975;54:405
- high frequency 1982;61:138 1983;62:122 (abstract) 1984;63:182
  - bronchoscopy, laryngoscopy and microlaryngeal surgery 1980;59:594
  - compared with conventional mechanical ventilation in lung injury 1982;61:323
  - effect on intracranial pressure (abstract) 1983;62:264
  - for tracheal resection in a child 1984;63:1039
  - gas mixing and dead space during HFPPV 1982;61:483
  - hemodynamic effects 1983;62:298
  - hemodynamic responses (abstract) 1983;62:265
  - high rates and low volumes 1980;59:567
  - ideal frequency and inspiratory time (abstract) 1983;62:249
  - intrapulmonary gas distribution, diagnostic bronchoscopy 1980;59:585
  - jet pulse characteristics 1982;61:293
  - lung surgery (abstract) 1982;61:180
  - management of terminal respiratory failure 1983;62:39
  - optional guidelines (abstract) 1982;61:222
  - oscillation 1980;59:577
  - safety without cuffed tube (abstract) 1982;61:195
  - tracheal reconstruction 1982;61:796
  - venous admixture 1982;61:735
  - ventilatory management of tracheomalacia 1983;62:538
  - ventilatory requirements during (abstract) 1982;61:175
- high frequency jet (abstract) 1984;63:208
  - cerebral and cardiopulmonary responses 1984;63:1065
  - changes in operating pressure 1984;63:19
  - during bronchoscopy 1984;63:957
- high-frequency
  - an alternative technique for sleeve pneumonectomy 1981;60:683
  - bronchofiberscopic 1981;60:68
  - cardiovascular function and gas exchange in dogs (abstract) 1981;60:256
  - effects of pulse duration, frequency and waveshape on airway pressures and $Pa_{CO_2}$ (abstract) 1981;60:252
  - gas exchange and (letter) 1981;60:363
  - intraoperative dual-mode independent lung 1981;60:118
  - positive-pressure ventilation in open-chest surgery 1981;60:324
- Hodgkin's disease, respiratory obstruction (case history) 1975;54:399
- hypocarbia, acute hypocapneic hypokalemia 1977;56:786
- hypoxia, reduction by dopamine 1982;61:333
- Innovar, and ventilatory depression, relationship to age and chronic obstructive pulmonary disease 1977;56:826
- inspired air temperature, immersion heater humidifiers 1976;55:331
- intermittent, mandatory 1975;54:41
- intermittent positive pressure, pattern (correspondence) 1978;57:146
- intermittent positive-pressure
  - effect of spontaneous vs controlled ventilation on alveolar halothane concentration in dogs 1977;56:32
  - effects of pattern, intrapleural pressure, and cardiac output 1977;56:88
- hypoxemia and hypocarbia 1976;55:555
- intraoperative, effect on postoperative arterial oxygenation 1975;54:427
- isoproterenol, cardiovascular effects and artificial heart implantation 1976;55:560
- I:E ratio (letter) 1984;63:1144
- jet
  - bronchofiberscope 1980;59:350
  - coaxial catheter for humidification during 1982;61:689
  - foot pedal control (brief reports) 1975;54:405
- mechanical
  - complicated by pneumothorax 1975;54:730
  - end-inspiratory pause 1976;55:122
  - fresh gas flow effects on minute volume (letter) 1984;63:619
- meperidine induced respiratory depression 1975;54:352
- meperidine, post-thoracotomy intercostal block 1976;55:542
- midazolam, respiratory depressant effects and lack of reversal with naloxone 1983;62:920
- monitoring minimal respiration 1975;54:232
- newborn hypoventilation 1975;54:38
- oncotic pressure, serum and hydrostatic pressure differences in critically ill patients 1982;61:496
- pediatric
  - changes in respiratory pattern affect dead space/tidal volume radio 1980;59:341
  - preextubation ventilatory measurements 1980;59:467

**Ventilation**—*continued*
  pneumatocele, larynx (brief reports) 1976;55:600
  positive end-expiratory pressure (abstract) 1984;63:242
    alternative for oxygenation maintenance (abstract) 1980;59:539
    therapy of acute respiratory failure 1980;59:831
    and continuous positive airway pressure, cardiopulmonary effects 1977;56:633
    device for anesthesia circuits 1977;56:578
    effect on carotid blood flow during cardiopulmonary resuscitation 1982;61:557
    effects of pattern, intrapleural pressure, and cardiac output 1977;56:88
    in brain and lung injury 1984;63:1065
    in experimental pneumonia 1979;58:208
    in pulmonary edema 1979;58:288
    magnetic valve for 1977;56:580
    measurement (correspondence) 1978;57:144
    postoperative arterial oxygenation 1975;54:427
    risk of paradoxical air embolism 1984;63:429
    selective, to dependent lung, improved oxygenation during thoracotomy 1977;56:26
    spontaneous 1977;56:627
    treatment of adult respiratory insufficiency 1975;54:31
  postoperative, recovery of pulmonary function 1981;60:46
  postoperative ventilatory failure, myopathic process 1975;54:523
  pulmonary gas exchange 1975;54:409, 1976;55:722
  pulmonary venous admixture changes with varying inspired oxygen 1976;55:688
  respiratory control, chronic obstructive lung disease 1980;59:865
  respiratory failure, choice between tracheostomy and prolonged translaryngeal intubation 1976;55:195.
  resuscitation, interposed abdominal compression 1982;61:645
  shunting, in pulmonary edema 1979;58:288
  surface tension of upper airway secretions 1975;54:602
  terminology, respiratory system terminology (letter) 1983;62:862
  transtracheal, emergency ventilation using available equipment 1982;61:867
  transtracheal (letter) 1983;62:457, 619, 168
  vibratory, respiration maintenance 1983;62:53
**Ventilators,** see Equipment
**Verapamil,** see
  Heart
  Pharmacology
**Veterinary anesthesia,** see Anesthesia, veterinary
**Viscosity,** see
  Anesthetics, gases, volatile
  Blood
  Oxygen
**Vomiting**
  (abstract) 1984;63:175
  antidiuretics, control during spinal anesthesia 1984;63:85
  antiemetics
    benzquinamide, cardiovascular effects 1979;58:189
    comparison of domperidone, droperidol, and metoclopramide after balanced general anesthesia 1979;58:396
    domperidone, effect on relaxant effect of atropine 1980;59:921
    domperidone, in treatment of postoperative 1978;57:700
    effectiveness of hydroxyzine compared with droperidol 1981;60:783
  incidence, after anesthesia and minor surgery 1977;56:674
**We salute**
  Alon P. Winnie 1975;54:600
  Douglas W. Eastwood 1976;55:185
  Edmond I. Eger II 1976;55:604
  Evan Lloyd Frederickson 1976;55:67
  Gertie F. Marx 1975;54:196
  Gordon M. Wyant 1975;54:425
  John Edward Steinhaus 1975;54:368
  Lawrence F. Schuhmacher, Jr. 1976;55:753
  Morris J. Nicholson 1975;54:55
  Paul Rudolph Dumke 1976;55:443
  Richard George Barton Gilbert 1976;55:892
**Wegener's granulomatosis,** see Complications
**Y-piece,** see Equipment

Supported By

Organon

ORGANON PHARMACEUTICALS
A Division of ORGANON Inc.
West Orange, NJ 07052

From ORGANON Research:

**NORCURON®**
(vecuronium bromide for injection)

**PAVULON®**
(pancuronium bromide injection)

**REGONOL®**
(pyridostigmine bromide injection)

SUCCINYLCHOLINE CHLORIDE
INJECTION USP